Studies towards the total synthesis of lomaiviticin and kinamycin, new entries towards locked nucleic acids, development of modifiable Rh(II) catalysts with high activity and synthesis of hydroxylamines by direct alcohol amination

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Dekan

Ein Gelehrter in seinem Laboratorium ist nicht nur ein Techniker; er steht auch vor den Naturgesetzen wie ein Kind vor der Märchenwelt.

Marie Curie (1867 - 1934)

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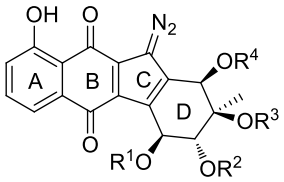
1 A unified approach towards kinamycin and lomaiviticin

1.1 Introduction

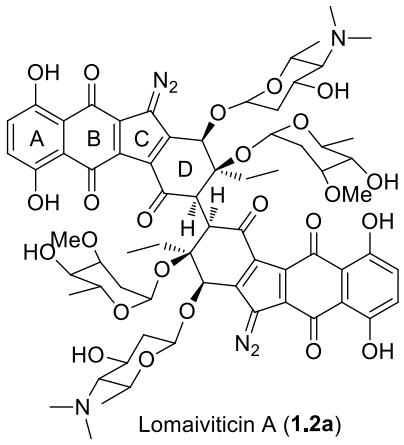
1.1.1 Isolation and properties

Kinamycin and lomaiviticin are two structurally related natural products which are distinct from most other natural products because they bear an unusual functional group: diazo.



Kinamycin (**1.1**)

	R^1	R^2	R^3	R^4
A:	H	Ac	Ac	Ac
B:	H	Ac	H	H
C:	Ac	H	Ac	Ac
D:	Ac	H	Ac	H
E	Ac	H	H	H
F	H	H	H	H
J	Ac	Ac	Ac	Ac



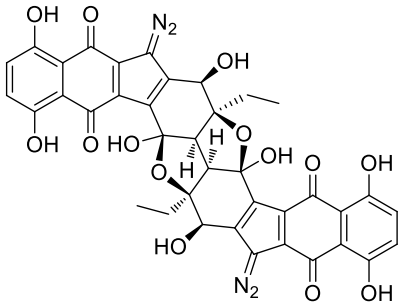


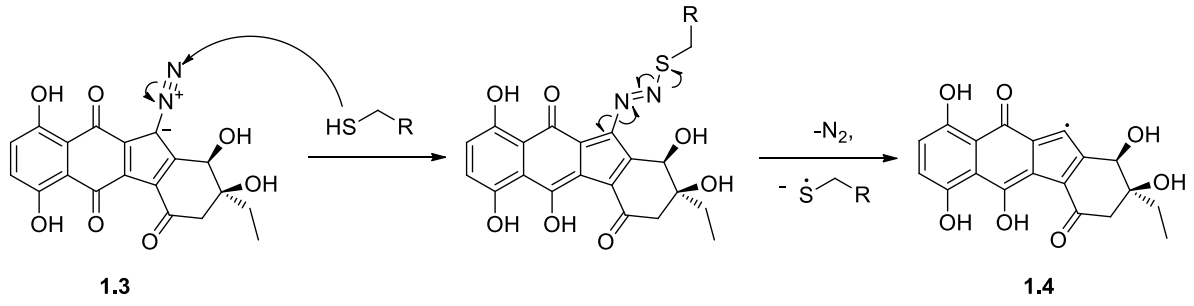
Figure 1-1 Structures of the most important representatives of the kinamycin family and lomaiviticin A and B.

Both molecules (**1.1** and **1.2**) show a similar molecular scaffold which is referred to as a diazofluorene: an aromatic (A) moiety with quinone (B) oxidation states, a central unsaturated five membered ring (C) with the diazo function and a six membered, highly oxidized ring (D) with three or four stereocenters. In regard to lomaiviticin's dimeric structure, kinamycin can be described as the corresponding monomer. Some differences apply though: The aromatic portion of kinamycin has an unsymmetrical pattern and the oxidation state is lower by an alcohol. The oxidized, saturated (D) ring has no ketone (or hydrate) and a methyl group is present instead of an ethyl.

Kinamycin (**1.1**) was isolated first in 1970 by Omura[1] in Japan from the culture broth of *Streptomyces murayamaensis* sp. nov. Also Omura reported just one year later an optimized isolation protocol and showed that **1.1** has strong antimicrobial activity against Gram positive bacteria but only weak anti-tumor activity.[2] Unfortunately, kinamycin's structure was initially reported to be a *N*-cyano moiety instead of a diazo, by chemical and spectroscopical means. A X-ray crystallographic analysis of the corresponding *p*-bromobenzoate revealed its real structure and absolute stereochemistry (as shown in Figure 1-1) in 1972.[3]

Lomaiviticin was isolated much later in 2001 by the group of Carter in the United States from the fermentation broth of what was thought to be *Micromonospora lomaivitiensis*, a strain of actinomycetes.[4] However, in 2011 it was found to be a *Salinispora* (*pacifica*) strain.[5] The lomaiviticins are exceptionally strong anticancer agents: Glycolate **1.2a** shows IC_{50} values in the 7.2 nM – 7.3 pM range against 24 cancer cell lines.

Herzon and coworkers studied the antiproliferative properties of kinamycins (**1.1A-F,J**), lomaiviticins (**1.2a-b**) and synthetic analogs.[6,7] They found that vinyl radicals (**1.4**) are likely the active species in DNA cleavage and nicking (Scheme 1-1). Dimeric diazofluorenes bind DNA with higher affinity than monomeric diazofluorenes and the binding mode described to be intercalation into the double helix. However, the intercalation itself could not promote cell death. This was concluded from experiments with lomaiviticin B, which showed the strongest intercalation properties but a comparably small DNA damaging activity. It was suggested that the D-ring carbonyl (see Figure 1-1) of the diazofluorenes is critical for DNA damaging. It is likely raising the oxidation potential, facilitating a nucleophilic attack at the diazo carbon for the formation of the active radical. In tissue culture, monomeric lomaiviticin aglycon **1.3** showed the highest DNA damaging activity (Scheme 1-1), which stands in contrast to *in vitro* studies where a synthetic, dimeric aglycon was most active. It was concluded that monomer **1.3** provides the optimal balance between reactivity, stability and cellular uptake. A welcome reality, regarding the significantly easier synthesis compared to its parent structure **1.2a**. It (**1.3**) thus bodes well for further studies of diazofluorenes as anticancer agents.



Scheme 1-1 Most active diazofluorene 1.3. in tissue culture and the proposed mechanism of forming reactive intermediates which result in DNA cleavage and nicking.

1.1.2 Previous total syntheses of kinamycin

The first total synthesis of kinamycin C was reported by Porco in 2006.[8] Their synthesis based on a convergent coupling of the aromatic backbone with the oxidized D-ring by Stille coupling and a subsequent acylation (Figure 1-2). The diazo was introduced in the last step by condensation of the ketone with *N*,*N'* –di TBS hydrazine and subsequent oxidation of the hydrazone by $PhIF_2$.

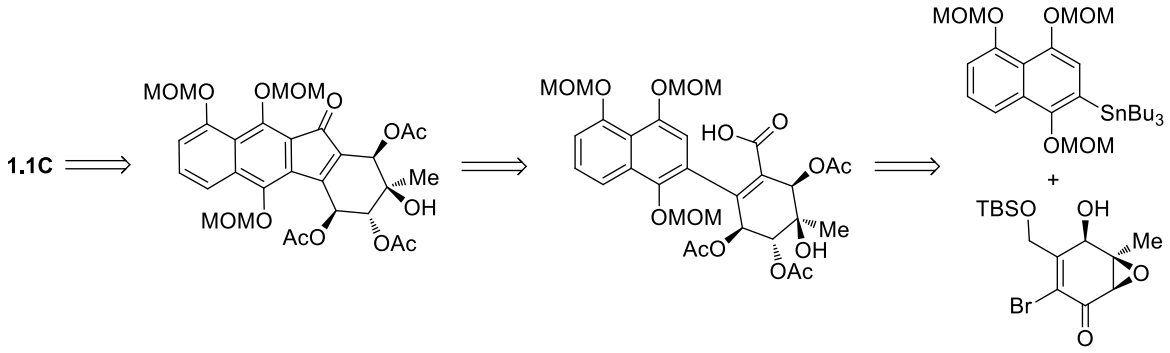


Figure 1-2 Retrosynthetic analysis of Porco's approach.

The first synthesis is certainly an important piece of work, however the approach lacks efficient and direct connections which resulted in a 26 step (23 linear steps) synthesis. Hence, the synthesis will not be discussed in details here.

The second synthesis was published by Nicolaou in 2007.[9] Their approach was similar to the previously reported one by Porco: convergent two step coupling of the aromatic backbone with the D-ring (Figure 1-3).

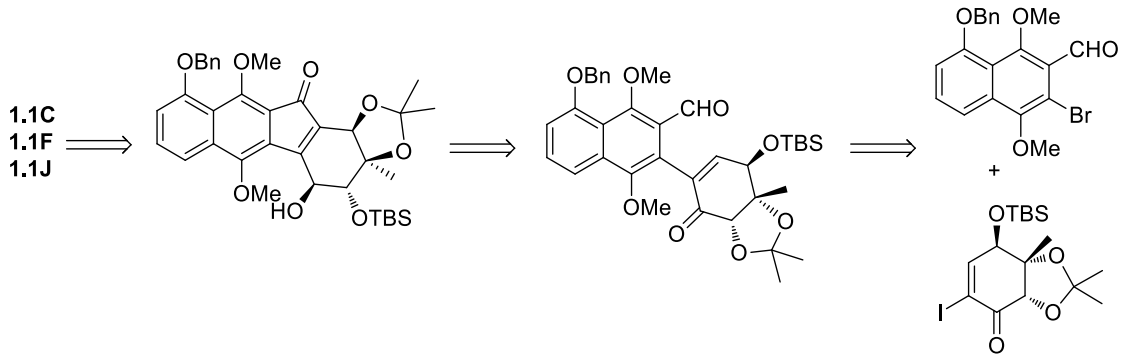
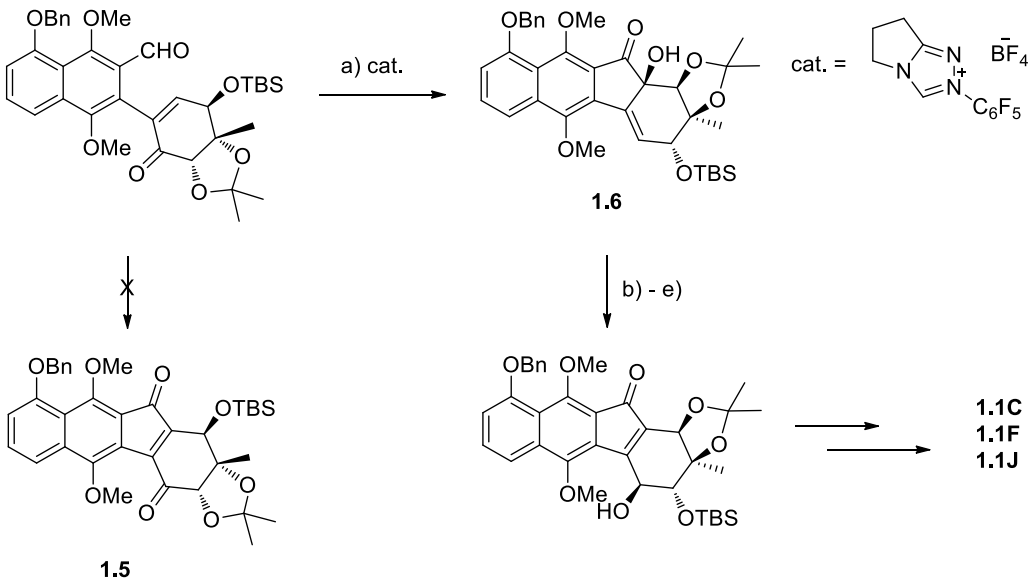


Figure 1-3 Retrosynthetic analysis of Nicolaou's approach.

Unfortunately, the planned triazol catalyzed Stetter reaction did not yield the expected 1,4 addition product **1.5** but the undesired 1,2 benzoin condensation product **1.6** (Scheme 1-2). This incident

elongated the reaction sequence by four more steps, nevertheless Nicolaou and coworkers managed to push through and finished the synthesis in 23 steps (18 linear steps).



Scheme 1-2 Stetter reaction in Nicolaou's synthesis with an unprecedented outcome. a) 0.2 eq cat., NEt_3, 45°C, DCM, 78%; b) Ac_2O, NEt_3, DMAP, rt, DCM, 95%; c) SmI_2, -78°C, MeOH/THF; d) NEt_3, rt, DCM, 81% over two steps; e) SeO_2, 110°C, 1,4-dioxane, 72%.

The introduction of the diazo function was as well performed by condensation and oxidation, but in contrast *N*-tosyl hydrazine was used and the oxidation was performed with CAN, which oxidized the methyl hydroquinone to the desired quinone at the same time.

The most recent and also by far the most efficient synthesis of the kinamycins was accomplished in the group of Herzon in 2010.[10] The key concept introduced by the previous syntheses, connecting the quinone and the D-ring in two steps was adopted by Herzon. The major difference, making their synthesis superior, was the step count of oxidizing and preparing the D-ring, together with the fact that the quinone never was reduced and protected as the methyl hydroquinone (Figure 1-4). Also the diazo group was introduced in a more efficient way (*vide infra*).

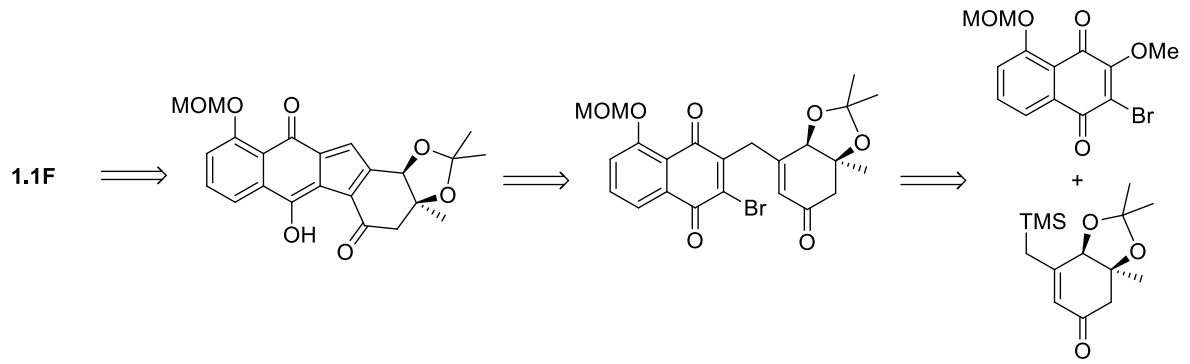
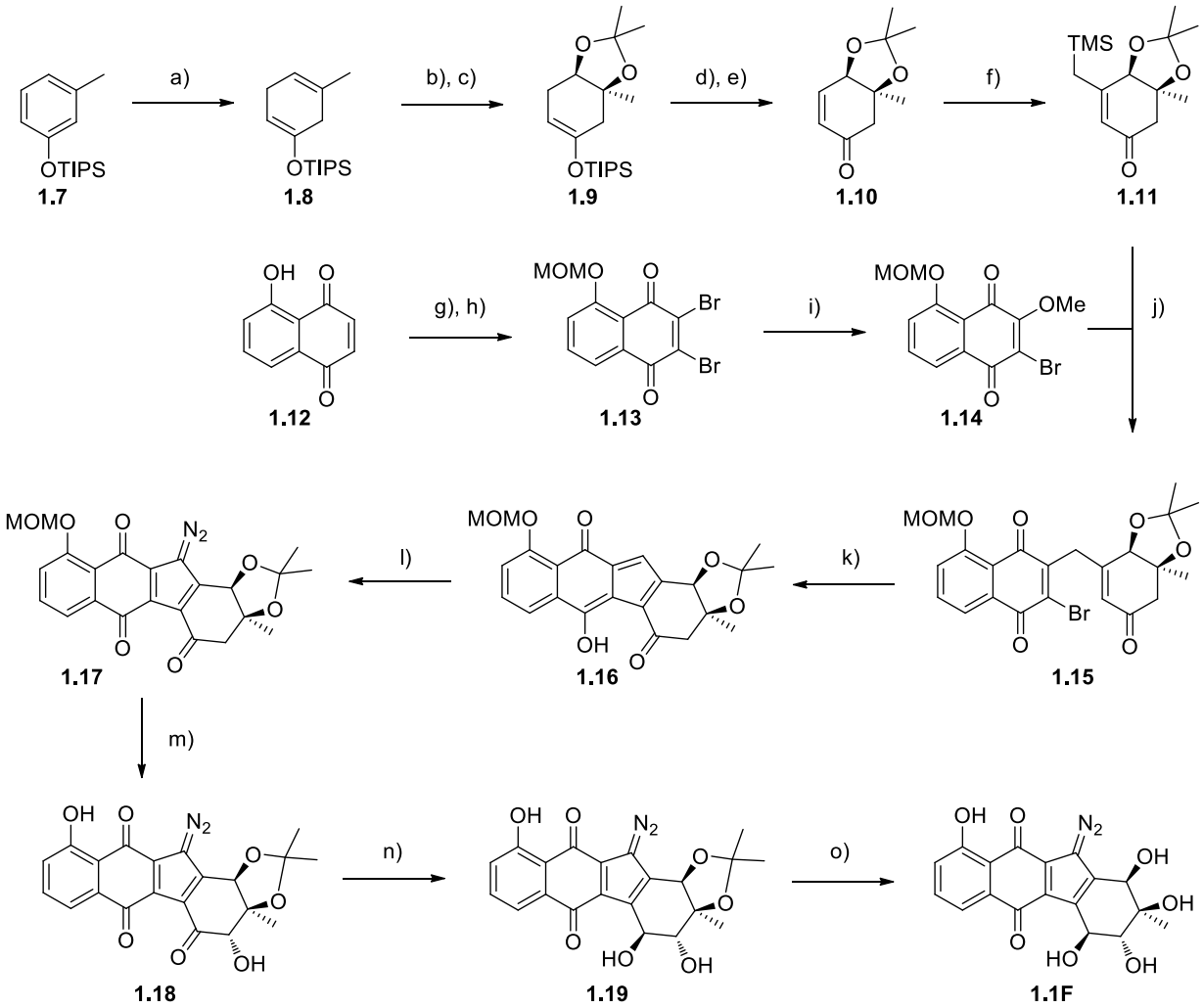


Figure 1-4 Retrosynthetic analysis of Herzon's approach.

Their synthesis commenced with the known TIPS protected *m*-cresol **1.7**, which was reduced by Birch reduction to the corresponding diene **1.8**. After enantioselective dihydroxylation of the more electron rich double bond and subsequent protection, dimethyl ketal **1.9** was obtained. Upon decomposition of the silyl enol ether and addition to phenylselenium chloride, oxidation and elimination afforded enone **1.10.** Michael addition of the TMS methyl Grignard reagent, trapping the intermediate as silyl enol ether and subsequent Saegusa-Ito oxidation gave the D-ring surrogate **1.11**.

Separately, juglone (**1.12**) was first brominated and then MOM-protected to give **1.13**, which was subsequently treated with Methanol under basic conditions to afford quinone **1.14**.

Enone **1.11** was activated by CsF, generating an allylic carbanion which added to quinone **1.14** in a 1,4-fashion and the intermediate was trapped as the corresponding TMS silyl enol ether. The methoxy was described to be crucial in order to obtain good yields. Upon treatment with $Pd(OAc)_2$, the quinone was restored giving access to the coupled moiety **1.15**. The following step was described as an attempt for a Heck cross coupling on the quinone, however Herzon also reported that the mechanism is not clear and a pentadienyl anion formation, electrocyclic ring closure and subsequent bromide elimination could have taken place. In any case, tetra cycle **1.16** was obtained and used to introduce the diazo moiety by nucleophilic addition to an electrophilic azide, giving diazo **1.17** in 99% yield.

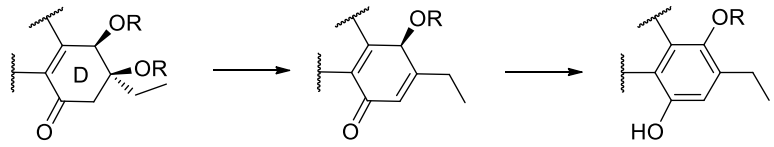


Scheme 1-3 Total synthesis of kinamycin F by Herzon: a) Na, NH_3, *t*-BuOH, -78°C, THF, 99%; b) AD-mix-β, $MeSO_2NH_2$, , -12°C, *t*-BuOMe, 55%, 66% ee; c) 2,2-dimethoxypropane, PPTS, 24°C, DMF, 88%; d) CsF, PhSeCl, -50°C, DMF, 69%; e) H_2O_2, pyridine, 24°C, DCM, 83%; f) $TMSCH_2MgCl$, CuI, HMPA, NEt_3, TMSCl, -30°C -> -78°C, THF; then $Pd(OAc)_2$, 24°C, MeCN, 88%; g) Br_2, AcOH, 120°C; h) MOM-Cl, $(i\text{-}Pr)_2NEt$, 0°C, DCM, 50% over two steps; i) Na_2CO_3, 65°C, MeOH, 96%; j) TASF(Et), -78°C, DCM, 79%; k) $Pd(OAc)_2$, polymer supported PPh_3, Ag_2CO_3, 80°C, toluene, 66%; l) TfN_3, $(i\text{-}Pr)_2NEt$, 24°C, MeCN, 99%; m) TIPS-OTf, $(i\text{-}Pr)_2NEt$, 0°C, DCM; then DMDO, -40°C, DCM-MeOH, 76%; n) BH_3-THF, -20°C, THF, 58%; o) 2.5 M HCl, -78°C -> 0°C, MeOH, 65%.

This reaction is superior to the condensation/oxidation procedure, because the carbon does not need the ketone oxidation state, the non-protected quinone is compatible and in fact exploited for the transformation and it is only one step. In the next step, an alcohol was introduced by Rubottom oxidation to form alcohol **1.18** and then the ketone was reduced by diastereoselective borohydride reduction, giving protected kinamycin F (**1.19**). In the last step, MOM and the ketal were removed by acidic hydrolysis in decent yield to furnish kinamycin F (**1.1F**). The deprotection was a brave step regarding the generally high acid sensitivity of diazo compounds.

1.1.3 Previous total syntheses of lomaiviticin

To date there is only one complete total synthesis of the lomaiviticins (**1.2**) reported and only of the aglycon lomaiviticin B (**1.2b**), which was done in the labs of Herzon in 2011 (*vide infra*).[11] Several research groups, famous for their complex natural product syntheses failed to get synthetic access to the lomaiviticins. Two different approaches were pursued: Building the dimeric core scaffold and then consecutive addition of building blocks on both sides, or synthesis of a monomer with eventual dimerization. In both cases, the steric hindrance between the two strongly substituted D-rings made the coupling difficult. In addition, the desired *beta* keto alcohol in the D-ring was reported to be prone to elimination, making it a difficult moiety to work with (Scheme 1-4).



Scheme 1-4 *beta* keto alcohol in the D-ring is prone to undergo elimination, leading to subsequent aromatization.

The first attempt at a dimeric core was published by Nicolaou in 2006.[12] In the end a 17 step synthesis resulted since several unexpected transformations took place during the sequence. Nevertheless, the first base was set, giving a clear picture of the problematics of the lomaiviticin core synthesis. The retrosynthetic analysis of the first attempt is shown in Figure 1-5, depicting the general strategy of Nicolaou and coworkers.

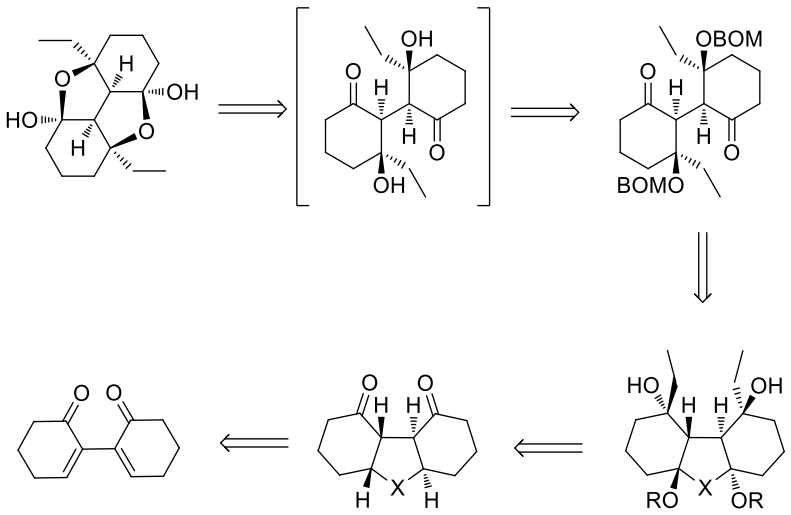
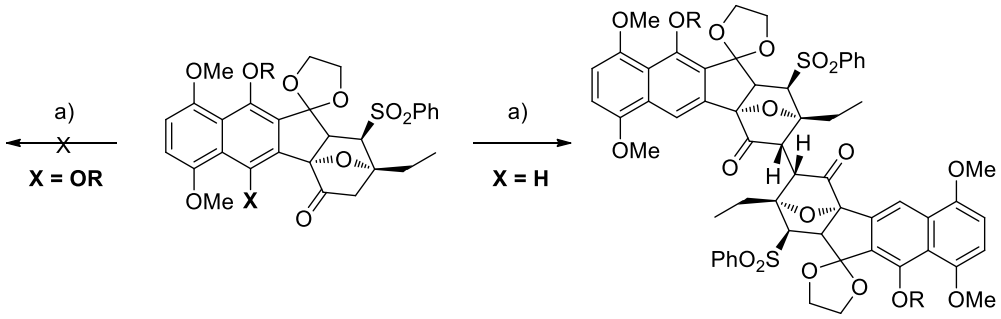


Figure 1-5 Retrosynthetic analysis of Nicolaous approach towards the lomaiviticin core. X = S or C-R.

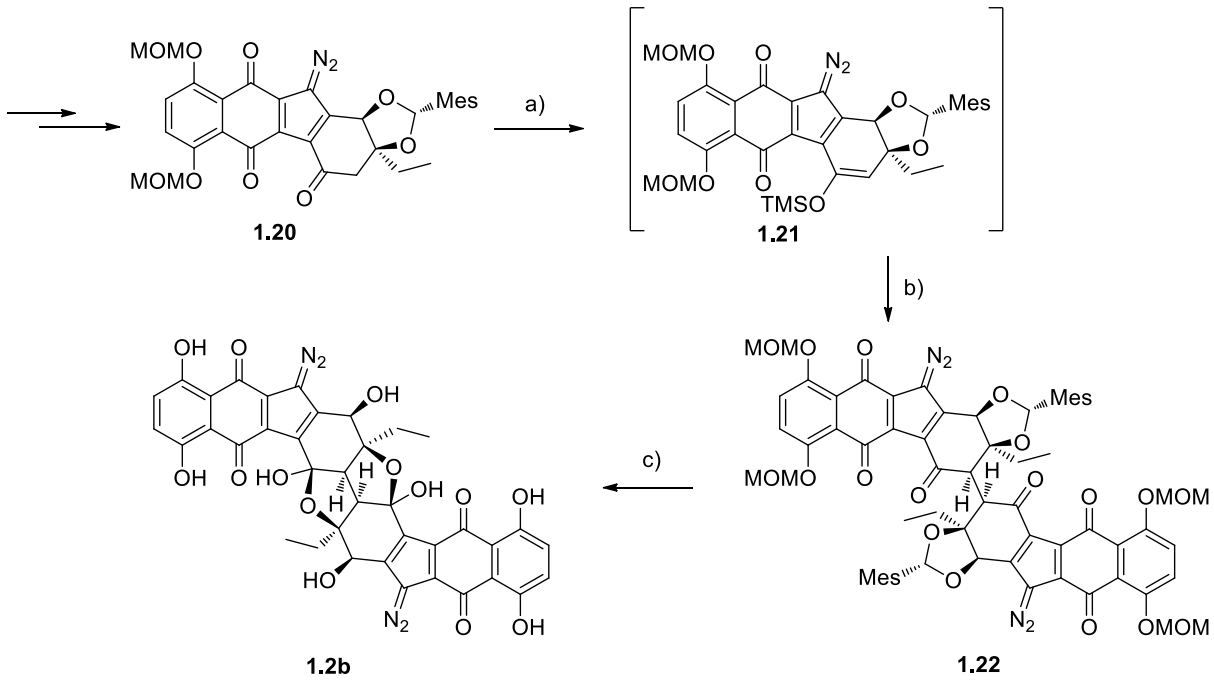
Nicolaou also reported a lomaiviticin monomer synthesis,[13] strongly based on the kinamycin synthesis (see 1.1.2), it was, however, never successfully dimerized.

Another noteworthy attempt was reported by Shair and coworkers in 2010.[14] An initial strategy of building the core[15] prior to adding the flanks failed and Shair was prompted to revise the strategy. After synthesizing a protected monomer, an end stage dimerization was attempted which initially failed as well and was rationalized by steric issues (X = OR, Scheme 1-5). But when the protected alcohol was removed (X = H), a high yielding enol dimerization was observed, being the first example of a full carbon frame synthesis of lomaiviticin. It was thus speculated by Shair whether the biosynthetic pathway could possibly go through a dimerization with a reduced scaffold, followed by a late stage oxidation.



Scheme 1-5 Shair's dimerization. Only the kinamycin type scaffold underwent the desired reaction. R = allyl. a) LiHMDS, HMPA, $Cp_2Fe(PF_6)$, -60°C, THF, 80%. Note: the stereochemistry is given as reported by Shair, which represents the other enantiomer than reported by Carter[4].

The first complete total synthesis was reported by Herzon and merits closer scrutiny. The strategy was based on the synthesis of kinamycin (*vide supra*) and was a late stage dimerization. The structural differences were only an ethyl group instead of the methyl on the D-ring and a mesityl acetal instead of a dimethyl acetal protected diol. Monomer **1.20** was first enolized and trapped as the corresponding TMS enol ether **1.21** before a manganese catalyzed dimerization was performed (Scheme 1-6). The transformation gave the desired *syn* product **1.22** in yields between 26-33%, where the orientation of the mesityl groups turned out to be crucial for the stereochemical outcome of dimerization. A final treatment with TFA and TBHP gave lomaiviticin B (**1.2b**). The dimerization was only achieved after an extensive screening of over 1500 conditions. Under most conditions only elimination of the vicinal alcohols and resulting aromatization of the D-ring was observed (compare to Scheme 1-4). The found manganese reagent was discussed to be optimal since its lewis acidity is very low due to a saturated ligand sphere and compared to other oxidants used for enol dimerization (e.g. $CuCl_2$ or CAN) it was completely soluble and stable in the reaction mixture.



Scheme 1-6 Herzon's dimerization giving access to lomaivitin B: a) NEt_3, TMS-OTf, DCM; b) then $Mn(F_3acacF_3)_3$, 26-33%; c) TFA, TBHP, -35°C, DCM, 39%.

For a comprehensive discussion on the syntheses of kinamycin and lomaiviticin, the reader is referred to the excellent review by Herzon.[5]

1.2 Retrosynthetic analysis

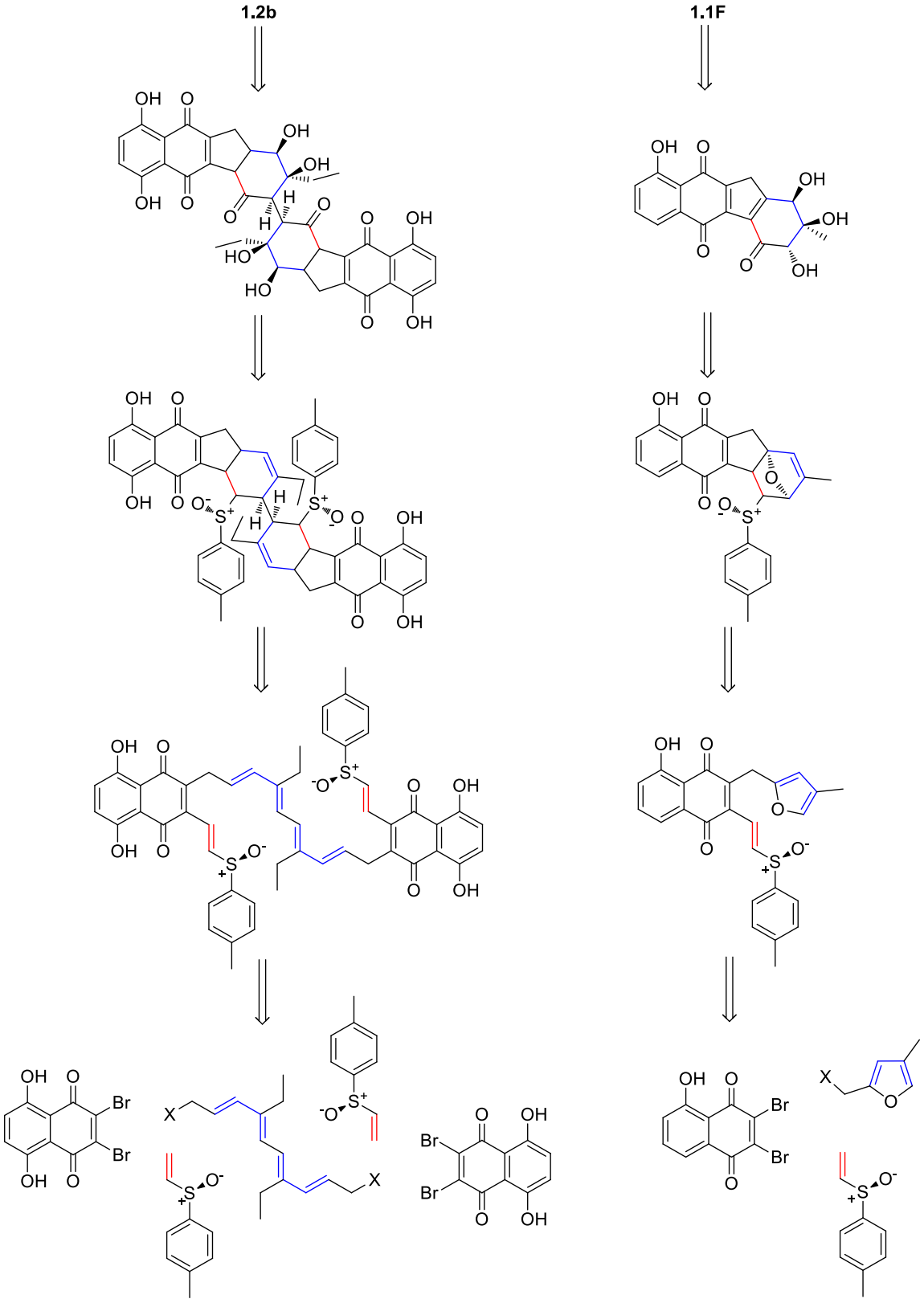


Figure 1-6 Retrosnthetic analysis of kinamycin F and lomaiviticin B.

We faced the retrosynthetic analysis of kinamycin and lomaiviticin with the knowledge provided in previous synthesis, but Herzon's synthesis of lomaiviticin had not yet been published. With regard to lomaiviticin we thus assumed that a dimerization is not possible due to steric constraints. Further, making a monomer would not have been very innovative. On the other hand, building up the core and extending on the flanks would likely become tedious and complex in the later stages. We thus envisioned building the carbon frame of lomaiviticin by Diels-Alder chemistry (Figure 1-6, left side) and add functionality on the scaffold once it was put together.

Coming from the natural product, we planned to introduce the diazo moiety last with the method shown by Herzon (Scheme 1-3). The vicinal diol could be introduced by dihydroxylation and the ketone made by Pummerer rearrangement and subsequent hydrolysis from a sulfoxide. The obtained carbon scaffold could be made by a Diels-Alder reaction, where the chirality of the sulfoxides controls the stereochemical outcome. The open chain system should be accessible by benzylic or allylic coupling of the central carbon chain with the aromatic moieties and the vinyl sulfoxides introduced by Heck cross coupling.

This approach would likely allow for the synthesis of kinamycin (Figure 1-6, right side) too. Again, the diazo was planned to be introduced last and the vicinal diol could be introduced by dihydroxylation of a double bond. The ketone which will be synthesized from the sulfoxide should be reduced *anti* to the adjacent alcohol, which is generated after a 5-membered ring ether cleavage. The additional oxygen was envisioned to be introduced by employing a furan as the diene. In a similar way to lomaiviticin, the single elements were planned to be put together by established cross coupling methods.

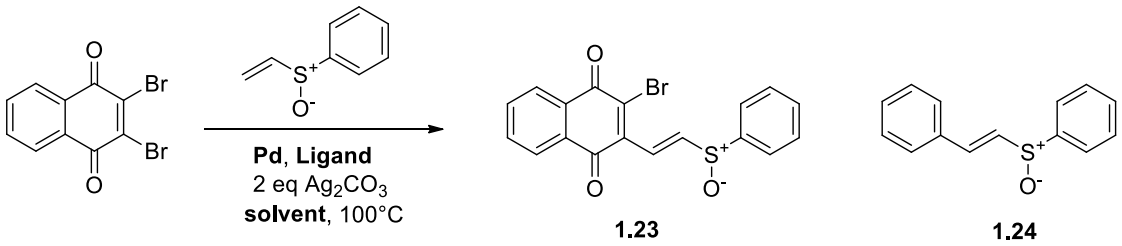
1.3 Synthesis

1.3.1 The lomaiviticin aromatic core and the development of Heck cross coupling with vinyl sulfoxides/sulfides/sulfones

The total synthesis of lomaiviticin began with the aromatic fragments. The first challenge was to introduce a vinyl sulfoxide on a quinone frame. After an extensive literature search it was found that although vinyl sulfoxides are chemically versatile, no general synthetic methods existed. A classic method is the *E* or *Z* selective reduction of alkynyl sulfoxides but only a few simple examples have been described.[16] A more recent Horner-Wittig approach leads to predominately *E*-configured products, but these are always contaminated with some *Z*-products (98:2 ratio in the best cases).[17] For us, whatever the downstream strategy was, a direct vinylation was crucial to maintaining a low step count in the total synthesis. A Heck vinylation was thus the reaction of choice. The sole reports of vinyl sulfoxide cross-couplings were by Carretero and coworkers[18] and Doucet, Santelli and coworkers[19]. The Doucet/Santelli procedure features an interesting tetradentate ligand-concept, but the forcing conditions (130 °C) and the complexity of the ligand have likely hindered the adoption of this approach by the synthetic community. The Carretero work represented the most general approach to date, but unmet challenges remained since their conditions employ excess aryl iodides and silver salts.

Herzon and coworkers reported in the case of kinamycin and lomaiviticin a Heck reaction with a quinone bromide (Scheme 1-3, step k), speculated about the actual mechanism though. Our own screening started thus with a quinone as well.

Table 1-1 Catalyst screening towards the Heck vinylation of 2,3 dibromonaphthoquinone with phenyl vinylsulfoxide.



1.23 **1.24**

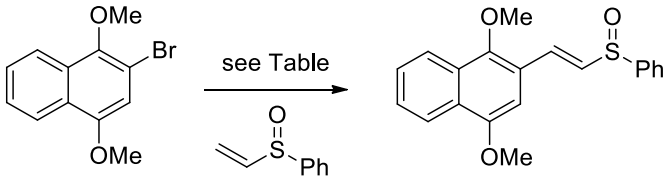
Entry	Pd source	mol %	Ligand	Ligand eq	Solvent	Yield **1.23**	Yield **1.24**
1	$Pd(OAc)_2$	50	dppp	0.5	DMF	0%	13%
2	$Pd(OAc)_2$	10	dppf	0.1	DMF	0%	8%
3	$Pd(PPh_3)_4$	10	-	-	DMF	0%	0%
4	$Pd(PPh_3)_4$	10	-	-	toluene	0%	0%
5	$Pd(PtBu_3)_2$	10	-	-	DMF	0%	3%
6	$Pd(OAc)_2$	100	PPh_3 on resin	1.5	DMF	0%	11%
7	$Pd(OAc)_2$	100	PPh_3 on resin	1.5	toluene	0%	20%
8	$Pd_2(dba)_3$	0.5	PPh_3 on resin	1.5	DMF	0%	0%
9	$Pd(OAc)_2$	40	TBAB	1	DMF	0%	8%
10	$Pd(OAc)_2$	10	TBAI	1	DMF	0%	0%

After employing Carretero's conditions[18] (Table 1-1, entry 1) a new product was obtained in small quantities but it was concluded to be the undesired side product **1.24**. This side product was already reported by Ruano[20] and stemmed from Pd(0) inserting into the S-C bond. Subsequent Heck reaction with a vinyl sulfoxide gave the quasi-homo coupled side product.

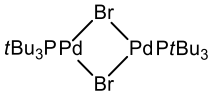
Screens were performed starting from Carretero's conditions, but no desired product **1.23** was obtained (entry 2-5). Also the employment of resin bound PPh_3 as reported by Herzon and increased Pd loading did not give access to the desired sulfoxide (entry 6-8). It was concluded that quinones are bad actors in cross coupling reactions. Mostly because the oxidation potential is high enough to oxidize Pd(0) to Pd(II), effectively shutting down the catalytic cycle. Further experiments with quinone and phosphine ligands only, revealed addition reactions. Phosphine free conditions (Jeffery conditions, entry 9-10) were thus employed, but didn't lead to the desired result.

We thus changed tack and a protected quinone in form of the corresponding dimethyl hydroquinone was considered. To further facilitate the screening, mono bromo species **1.25** was chosen as the substrate for the second investigation towards the vinylation with sulfoxides.

Table 1-2 Screening and optimization of the catalyst system with dimethyl hydroquinone



1.25 **1.26**

Entry	Catalyst	Base	Solvent	Yield **1.26**
1	$Pd(OAc)_2$	Ag_2CO_3	DMF	0%
2	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	0%
3	$Pd(PtBu_3)_2$	Cs_2CO_3	DMF	11%
4	$Pd(PtBu_3)_2$	Ag_2CO_3	DMF	0%
5	$Pd(PtBu_3)_2$	Cs_2CO_3	dioxane	0%
6	$Pd(PtBu_3)_2$	NCy_2Me	dioxane	60%[a)]
7	$Pd(PtBu_3)_2$	DIPEA	dioxane	20%[a)]
8	$Pd(PtBu_3)_2$	DBU	dioxane	0%[a)]
9	$Pd(PtBu_3)_2$	Pyridine	dioxane	15%[a)]
10	$Pd(PtBu_3)_2$	NEt_3	dioxane	93%
11		NEt_3	dioxane	0%[a)]

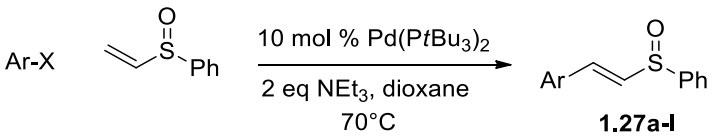
[a)] represents % conversion according to ^{1}H-NMR; an isolated yield was not determined in these cases.

The investigations began again by testing Carretero's conditions.[18] These conditions, however, failed to deliver any product (Table 1-2, entry 1) and also did not lead to oxidative addition into the Ar-Br bond. While conditions with $Pd(PPh_3)_4$ (entry 2) also failed to yield any desired coupling, a first hint of success was achieved with the $Pd(PtBu_3)_2/Cs_2CO_3$/DMF combination (entry 3).[21] Inorganic bases mostly gave mostly dehalogenated product, if oxidative addition was observed. Hence, organic amine bases were screened: Buchwald and Fu have shown that the hindered amine base NCy_2Me can have a dramatic accelerating effect on Heck couplings.[22,23] As seen in entry 6, NCy_2Me was superior to inorganic bases in sulfoxide cross-coupling but still did not deliver complete conversion. A screen of other common amine bases led to even lower conversions (entries 7-9). Triethylamine was the sole exception, proving uniquely effective for efficient coupling (entry 10: >98% conversion, 93% isolated yield). Curiously the palladium(I) dimer complex that has proven so active as a precatalyst in other forms of cross-coupling,[24] was completely unreactive with vinylsulfoxides (entry 11).

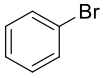
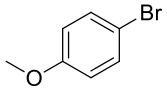
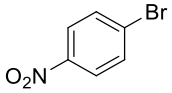
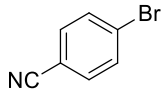
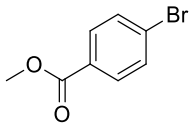
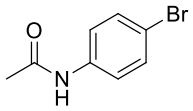
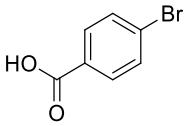
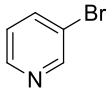
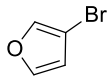
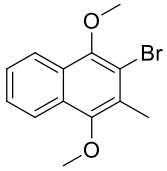
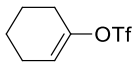
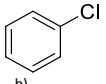
With an effective catalyst system identified the first big hurdle was overcome and the following steps of the total synthesis could be tackled. Nevertheless, since the Heck reaction with vinyl sulfoxides

was not well described in literature, we were curious whether our conditions (Table 1-2, entry 10) were generally applicable and could be of use for the synthetic community. We thus started to explore the scope of the reaction with electronically and sterically diverse aryl bromides (Table 1-3).

Table 1-3 Scope of the Heck reaction with phenyl vinyl sulfoxide



1.27a-l

Entry	Ar-X	Time [h]	Conversion	Yield / Product
1[a]		0.5	>98%	82% / **1.27a**
2		2	>98%	73% / **1.27b**
3[a]		2	>98%	80% / **1.27c**
4		1	90%	76% / **1.27d**
5		2	>98%	80% / **1.27e**
6		4	>98%	88% / **1.27f**
7		2	>98%	80% / **1.27g**
8[b]		2	>98%	58% / **1.27h**
9		40	>98%	88% / **1.27i**
10		24	40	37% / **1.27j**
11		1	>98%	69% / **1.27k**
12		6	>98%	23% / **1.27l**
13		32%	<2%	-

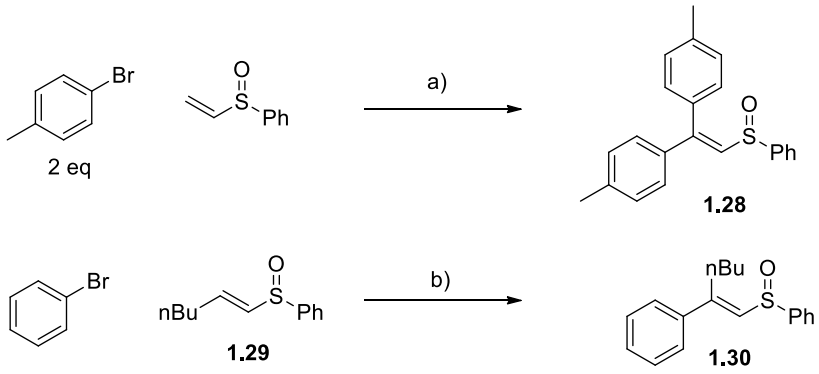
[a] 5 mol% $Pd(PtBu_3)_2$. [b] 4 eq. NEt_3

Phenyl bromide underwent complete vinylation in 30 minutes, delivering 82% isolated yield. Electron rich systems such as *p*-methoxybromobenzene or *o*-bromotoluene were successfully converted in good yields (73%, 80% respectively). It is noteworthy that unfunctionalized aryl bromides (entry 1) or those with only aliphatic functionalization (entry 3) could be run with 5 mol% catalyst, but heteroatom substituted systems required 10 mol% catalyst loading to reach full conversion in a reasonable time.

Electron poor substrates (entries 4-8) furnished the desired products in good yields as well: *p*-cyano, *p*-methanoate and *p*-acetamido bromobenzene underwent the transformation with full conversions and yields of 80% and above (entries 5-7). Reaction of nitro substituted aryl bromide was sluggish, reaching only 90% conversion under the standard conditions (entry 4). *p*-Bromo benzoic acid underwent full conversion, although four equivalents of triethylamine were needed to cope with the additional acidic protons. More challenging heterocyclic aryl bromides as well as sterically encumbered substrates were also tolerated. 3-Bromo pyridine (entry 9) was converted into the desired product with 88% yield, although forty hours were required for complete conversion. 3-Bromo furan was the most poorly accepted bromide substrate, delivering only 40% conversion and 37% yield after 24h. Entry 11 represents a challenging substrate in terms of sterics and electronics, and yet full conversion and 69% yield was attained.

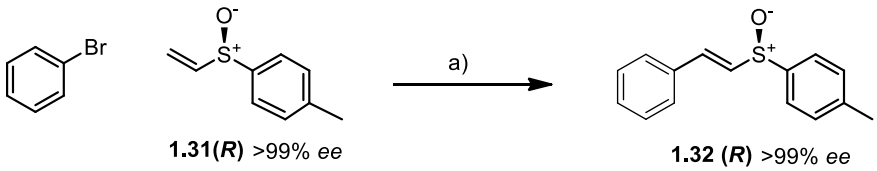
Entry 12 indicates that triflates are also viable cross-coupling partners. In this case the vinyl triflate was fully consumed but unreacted sulfoxide was still present. Although this suggested that some of the triflate decomposed during the reaction, 23% yield was still achieved. To our surprise phenyl chloride failed to react, although examples with aryl chlorides and different Heck acceptors are known with $Pd(P\mathit{t}Bu_3)_2$.[22] We therefore tested the known Heck coupling of 4-chloroacetophenone with styrene[22] and found that the presence of phenyl vinylsulfoxide inhibited the normal Heck coupling. This result suggested that one of the steps in the catalytic cycle with aryl chlorides was perturbed in the presence of sulfoxides.

The cross-coupling system is exceptionally active with aryl bromides and allowed the formation of symmetric and unsymmetric trisubstituted olefins (Scheme 1-7). For symmetrical olefins, employing 2 equivalents of the aryl bromide at elevated temperature afforded the desired product in good yield (top line Scheme 1-7). The ability to select between the single or double Heck products by simply adjusting stoichiometry should prove of considerable synthetic value.



Scheme 1-7 Synthesis of symmetric (top) and unsymmetric (bottom) trisubstituted olefins. a) Pd(P*t*Bu$_3$)$_2$, NEt$_3$, dioxane, 100°C, no yield due to unseparable impurities; b) Pd(P*t*Bu$_3$)$_2$, NEt$_3$, dioxane, 70°C, 50%.

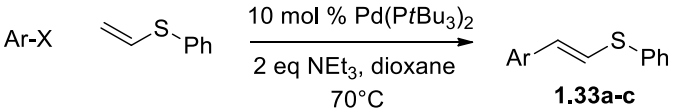
The cross-coupling conditions are compatible with sulfoxide stereocenters since enantiopure *R*-tolyl vinyl sulfoxide **1.31(*R*)** leads to enantiopure product **1.32(*R*)** (Scheme 1-8). This result bodes well for using the coupling method to introduce sulfoxide-based chiral auxiliaries and was a very important result for the planned total synthesis of kinamycin and lomaiviticin.



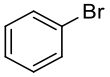
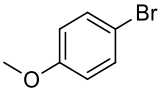
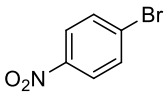
Scheme 1-8 Sulfoxide stereocenters are unaffected in the Heck coupling. a) Pd(P*t*Bu$_3$)$_2$, NEt3, dioxane, 70°C, 90%.

Although vinyl sulfoxides were our primary interest, we were aware that sulfones and sulfides are also poorly tolerated in Heck coupling. For example, vinylsulfides in particular have only been employed in two cases that we could find.[25,26] Nevertheless employing the conditions we identified led to complete conversion of phenyl vinylphenylsulfide in two cases and 90% conversion in the case of nitrobromobenzene (Table 1-4, entry 3), delivering the products **1.33a-c** in 68% - 73% yield (Table 1-4). It is noteworthy, that product **1.33c** was the first and only example where not only *E* but also small amounts of the *Z* isomer were observed.

Table 1-4 Additions to vinyl sulfides are also efficient.



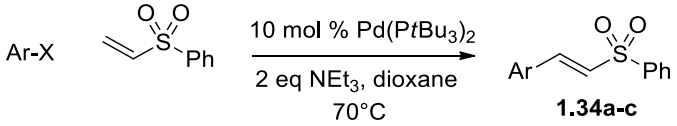
1.33a-c

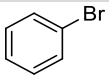
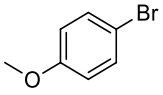
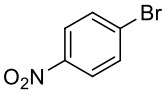
Entry	Ar-X	Time [h]	Conversion	Yield / Product
1		3	>98%	73% / **1.33a**
2		2	>98%	68% / **1.33b**
3		4	90%	68% / **1.33c**

Interestingly, the system developed by Yoshida[26] for pyrimidine-directed Heck coupling of vinylsulfides is almost identical to the system we describe here and yet they required aryl iodides to achieve cross-coupling. It is not clear why in Yoshida's case the ostensibly more reactive iodides also require a directing group to activate the olefin substrate, whereas we saw that less reactive aryl bromides can be efficiently cross-coupled to vinylsulfides lacking a directing group. It could be that although aryl iodides are superior in oxidative addition, the iodide anion generated in the process is deleterious to other steps of the catalytic cycle. Solvent effects may also be a factor as they used toluene and we used dioxane; but Fu has shown that with aryl chlorides there is a marginal difference between these two solvents in Heck reactions.[21]

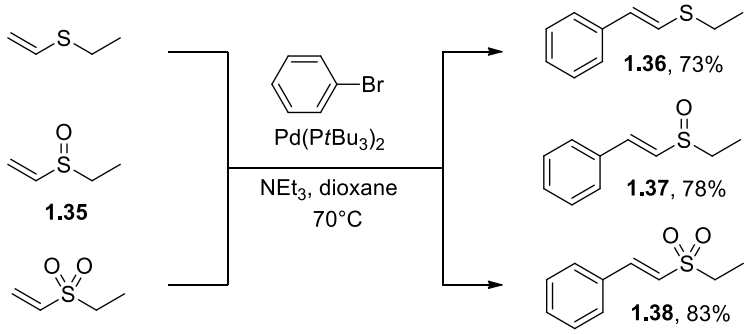
If phenyl vinylsulfone were accepted as a cross-coupling partner, then olefins bearing the whole set of sulfur oxidation states would be accessible through one unified protocol. Indeed phenyl vinylsulfone was efficiently coupled under the optimized conditions to deliver the sulfones **1.34a-c** in 74-92% yield (Table 1-5).

Table 1-5 Additions to vinyl sulfones are also efficient



Entry	Ar-X	Time [h]	Conversion	Yield / Product
1		3	>98%	88% / **1.34a**
2		2	>98%	92% / **1.34b**
3		4	>98%	74% / **1.34c**

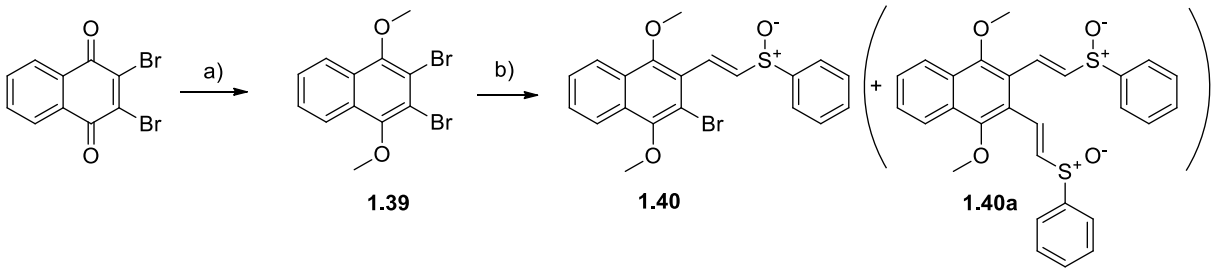
In order to broaden the scope of the described methodology even further, we employed the catalyst system to ethyl vinyl sulfide/sulfoxide (**1.35**)/sulfone, which sport in case of the sulfoxide and sulfone acidic alpha protons. In all three cases the desired product was furnished in good yield (Scheme 1-9) with only 5 mol% catalyst.



Scheme 1-9 Additions to ethyl vinyl sulfide, sulfoxide and sulfone broadens the scope.

Vinyl sulfur compounds in their various oxidation states are challenging substrates for Heck cross-couplings. The generality of the $Pd(PtBu_3)_2/NEt_3$ system opens up this class of molecules for further synthetic exploitation. Some practical points merit mention: the catalyst is commercially available, the procedure is operationally simple, and reaction times are shorter than with other catalyst systems (typically 2h vs 24h with other catalysts). A disadvantage is the relatively high catalyst loading required (5-10%) for complete conversion. Even with low turn-over numbers, however, the present catalyst system filled a void in Heck cross-coupling chemistry and should find broad applicability in the synthetic community.

After gaining access to Heck-coupled vinyl sulfoxides, we wanted to apply the methodology on a bromonaphthoquinone model system for lomaiviticin (**1.39**), which was made in two steps from commercial material (The fully oxidized naphthazarine moiety, A and B ring Figure 1-1, was planned to be introduced into the total synthesis once further steps were worked out). Sulfoxide **1.40** was obtained under the developed conditions, however it was found that the vinyl sulfoxide in the product activated the second bromide towards oxidative addition and thus led to the double Heck product **1.41** in significant amounts (Scheme 1-10). The change of solvent to toluene and lowering the temperature to 50°C had beneficial effects but the only effective measure was to employ five equivalents of the dibromoquinone **1.39**. Nevertheless, during the transformation no decomposition reactions took place and **1.39** eluted significantly earlier on normal phase silica gel, which allowed the reisolation of its excess with almost no loss.

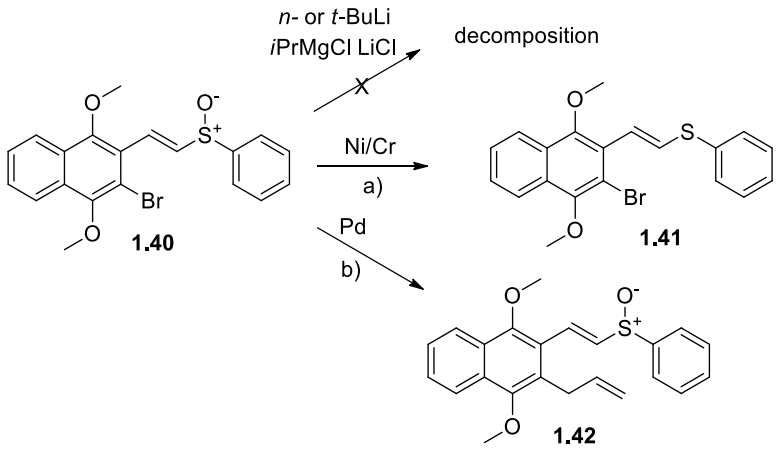


Scheme 1-10 Application of the found conditions to the model system of the flanks of lomaiviticin. a) $Na_2S_2O_4$, H_2O, Et_2O, EtOAc, rt; then NaH, MeI, DMF, rt., 64% over 2 steps; b) 5 eq 1.39, *rac.* phenyl vinyl sulfoxide, NEt_3, 15 mol% $Pd(PtBu_3)_2$, toluene, 60°C, 69% after reisolation of 1.39.

1.3.2 Investigations towards the coupling of the aromatic flanks with the central carbon chain

In order to couple two model system flanks (**1.40**) with a tetraene, several reaction types were considered: nucleophilic addition of the hydroquinone to an aldehyde, Nozaki-Hiyama-Kishi reaction of the hydroquinone with an aldehyde or palladium catalyzed cross couplings of the quinone and an allyl boronic acid / stannane.

Lithium halogen exchange with *n*-BuLi or *t*-BuLi at various temperatures only led to decomposition. The same was observed with *i*PrMgCl LiCl complex, however in this case at least isopropyl phenylsulfoxide was found by GC-MS, indicating addition of the alkyl grignard to the sulfoxide, giving a hint why the lithium halogen exchange could have failed (Scheme 1-11).



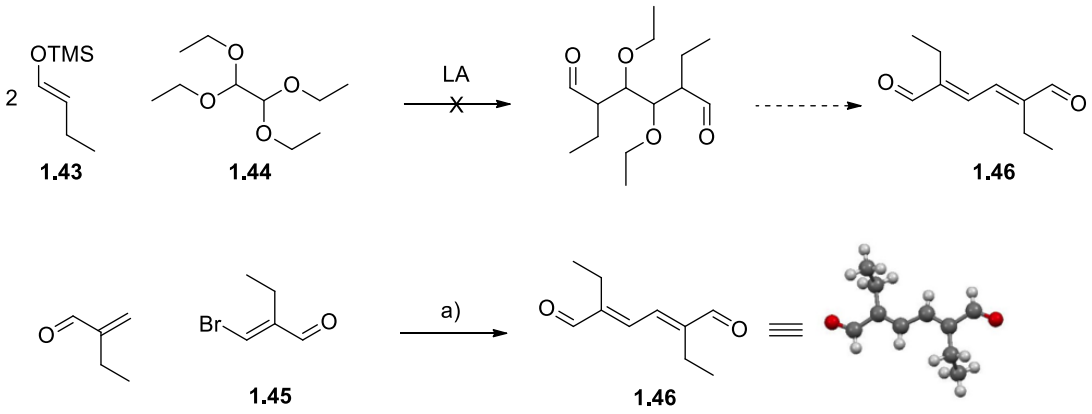
Scheme 1-11 Unsuccessful and successful attempts for the second coupling. a) sorbaldehyde, $NiCl_2$, $CrCl_2$, DMF, 40°C, 41%; b) allyl-$SnBu_3$, 10 mol % $Pd(PtBu_3)_2$, toluene, 60°C, 41%.

The employment of $NiCl_2$ and $CrCl_2$ in a Nozaki-Hiyama-Kishi reaction led to clean transformation of hydroquinone **1.40**, but it turned out that under these conditions no insertion into the Ar-Br bond occurred but the sulfoxide was selectively reduced to the corresponding sulfide **1.41**. On the other hand the cross coupling between **1.40** and allyl tributylstannane was smooth and gave the desired sulfoxide **1.42** without event. This test reaction set the stage for the synthesis of the tetraene linker, containing allyl stannanes for the coupling.

1.3.3 Lomaiviticin central carbon chain

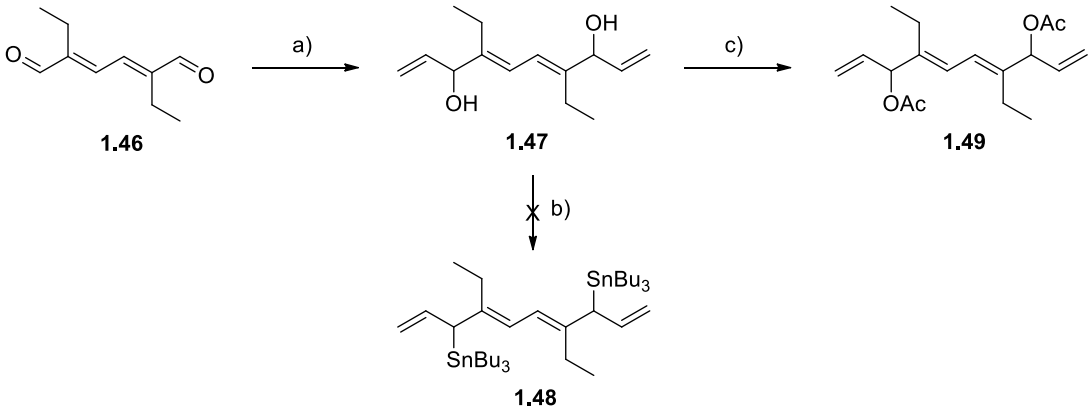
The next step was to find a synthetic route to the central carbon chain, which was planned to be employed as a twofold diene in the Diels-Alder reaction (Figure 1-6, bottom left).

First attempts employing a condensation reaction which was inspired by the work of Isler in the field of carotenoid synthesis[27] failed (Scheme 1-12, top), so we turned again to a Heck approach. With Jeffery's "ligand less" conditions, which were applied for Heck reactions with Michael acceptors before[28,29], it was indeed possible to couple two ethyl acrolein fragments to build the desired diene **1.46** (Scheme 1-12, bottom). The required *trans* double bond of **1.46** was confirmed by crystal structure analysis.



Scheme 1-12 Attempted Lewis acid catalyzed condensation (top) and successful Heck reaction (bottom). a) 0.1 eq $Pd(OAc)_2$, TBAC, DMF, rt, 65%.

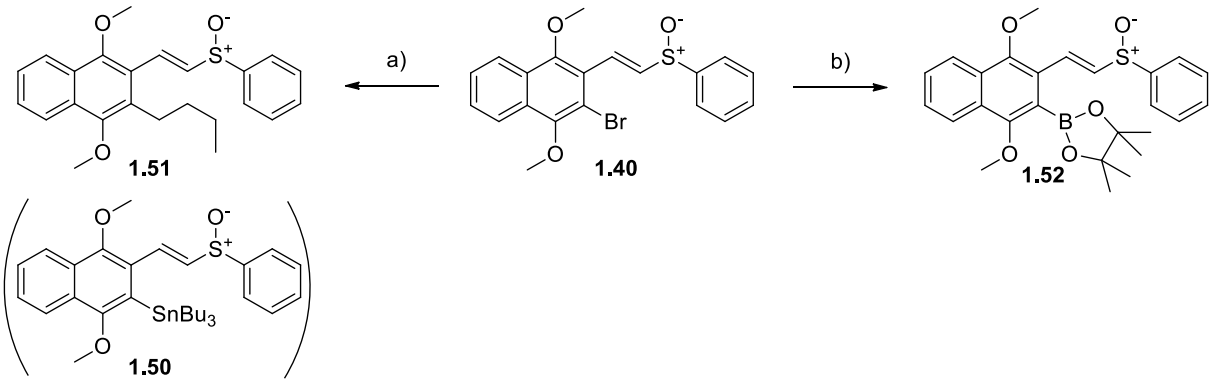
The elongation of the diene to the required tetraene was done by a twofold vinyl Grignard addition and gave the desired diallyl alcohol **1.47** in 65% yield (Scheme 1-13). Since a Stille allylation was planned, the actual position of the stannane seemed not to matter. After the transmetalation an isomerization to the sterically less hindered terminal species was expected. The allyl alcohol **1.47** was thus attempted to be transformed into its corresponding allyl stannane **1.48** by a procedure developed in the group of Brückner[30], however after several attempts it was not possible to isolate the desired allyl stannane. Since a tedious synthesis of an activated tetraene was not desired, we decided to switch the roles and add the functional group required for the transmetalation on hydroquinone **1.40** (see 1.3.4) and prepare the allyl alcohol for the oxidative addition. Secondary allyl acetates were reported to undergo oxidative addition with Pd(0) catalysts and complete transposition to the terminal allyl complex, which in turn undergo cross coupling reactions.[31] With this in mind we acetylated **1.47** and obtained the corresponding diacetate **1.49** in good yield.



Scheme 1-13 allylation, attempted stannylation and successful acetylation. a) vinyl-MgBr, THF, 0°C, 54%; b) *n*-BuLi, MsCl, then $LiSnBu_3$; c) Ac_2O, NEt_3, DMAP, DCM, rt, 84%.

1.3.4 Coupling of the aromatic flanks with the central carbon chain

With the diallyl acetate **1.49** in hand, hydroquinone **1.40** needed to be prepared as the transmetalation partner. Since the test allylation in Scheme 1-11 was successful with a stannane, the first attempt was to turn **1.40** into aryl stannane **1.50**. Full conversion to a new product was observed after treating **1.40** with Pd(0) and a distannane (Scheme 1-14). The crude NMR spectra looked promising, however upon isolation, the butyl groups did by far not integrate in agreement with the rest of the molecule. Characterization by MS revealed it to be butyl hydroquinone **1.51**. Because stannanes can either be introduced by addition of alkyl lithium species, which was not possible in our case (see Scheme 1-11), or by Pd(0) catalysis we had no other options than trying to optimize the reaction. Unfortunately, in any case butyl **1.51** or simply dehalogenated product **1.26** were the only products generated in the reactions.

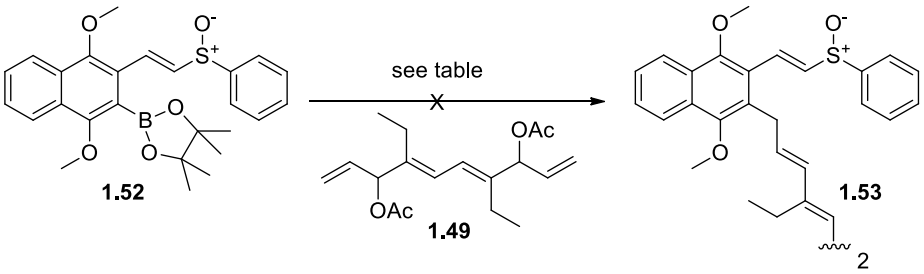


Scheme 1-14 Attempted stannylation leading to a butyl transfer and successful borylation by Pd(0) cross coupling. a) Sn_2Bu_6, $Pd(PtBu_3)_2$, toluene, 70°C; b) H-BPin, NEt_3, $Pd(PtBu_3)_2$, dioxane, 100°C, 31%.

As a consequence, we changed from Stille to Suzuki cross couplings and tried to introduce a boronic acid or a respective pinacol ester by Pd(0) catalysis. After a small screening for conditions, Masudas protocol[32] with H-BPin gave roughly 50% of the desired boronic acid pinacol ester **1.52**, while the other 50% were dehalogenated **1.26**. On a preparative scale a rather bad yield of 31% was obtained but it allowed continuing with the study. The most common procedure with B_2Pin_2 by Miyaura[33] failed.

For the coupling of pinacole ester **1.52** with dially acetate **1.49** a screening was started which is presented in Table 1-6.

Table 1-6 Screening towards the allylic suzuki coupling to connect the aromatic flanks of the lomaiviticin scaffold.



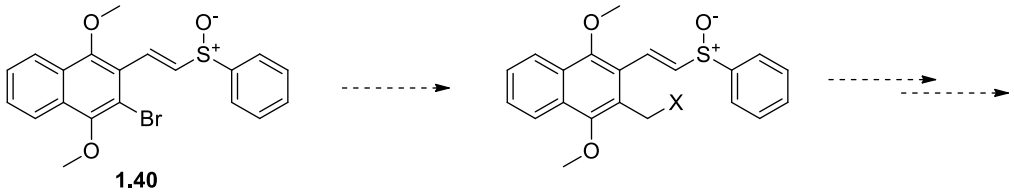
Entry	Catalyst	Solvent	Additive	Ox. add.	Transmet	Coupling
1	$Pd(PtBu_3)_2$	dioxane	Cs_2CO_3	-	yes	-
2	$Pd(PPh_3)_4$	dioxane		yes	-	-
3	$Pd(PPh_3)_4$	diox/tol 1/1	Cs_2CO_3	yes	-	-
4	$Pd(PtBu_3)_2$	toluene	Cs_2CO_3	yes	yes	-
5	$Pd(PtBu_3)_2$	toluene		yes	yes	-

Under most conditions employed, oxidative addition into the allyl acetate was observed (entry 2-5), which was concluded from ^{1}H NMR aliquot spectra. In all these cases, however, only the absence of **1.49** was observed and no new corresponding products. Under two of these conditions also transmetalation with **1.52** was observed (entry 4-5) but only the corresponding protonated side product **1.26** formed according to ^{1}H NMR aliquot spectra.

After this screening we had to conclude that diallyl acetate **1.49** was not a suitable coupling partner via oxidative addition. It is likely that the oxidative addition occurred in the desired manner, but the Pd-allyl complex reacted via undesired decomposition pathways instead of acting as a coupling partner.

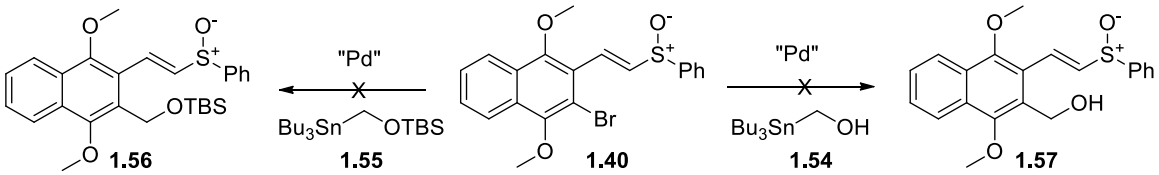
1.3.5 Change to a benzylic coupling and the transition to kinamycin

With the knowledge that probably Pd catalyzed reactions were the only possibility and that allylic couplings can be rather difficult to employ, we turned to an alternative plan based on a benzylic oxidative addition (Scheme 1-15).



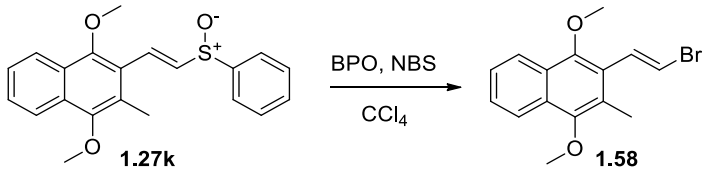
Scheme 1-15 Envisioned transformation to a benzylic halide for subsequent cross coupling

The first step in the new synthesis plan was thus to introduce the additional benzylic carbon. Tributyltin methanol **1.54** was thus synthesized according to a literature procedure in one step.[34] This reagent was employed previously to introduce benzylic alcohols.[35] In our case though, no desired benzyl alcohol formation was observed , even if TBS protected stannane **1.55** was employed (Scheme 1-16)**.**[36]



Scheme 1-16 Unsuccessful methanol homologation by Stille reaction.

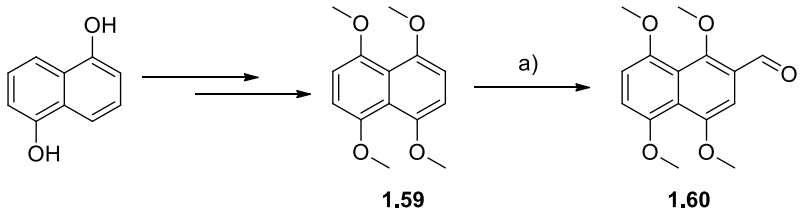
In another attempt a benzyl bromide was envisioned to be introduced by a Wohl-Ziegler reaction. Very much to our surprise though, an unexpected product formed exclusively, which's spectroscopic data was not in agreement with the expected bromide. Careful analysis revealed the formation of vinyl bromide **1.58**. It is noteworthy that the *E* configuration was obtained as single isomer, not a matter of course in a radical mechanism (Scheme 1-17). The synthesis of **1.58** makes the methodology presented in 1.3.1 even more valuable because the sulfoxides can be transformed to another versatile functional group after introduction by cross coupling.



Scheme 1-17 Unexpected radical cleavage of the C-S bond and *E*-selctive bromination under Wohl-Ziegler conditions.

For the planned total synthesis though, the outcome was of lesser value and we thus had to look yet for another alternative to introduce a benzylic carbon.

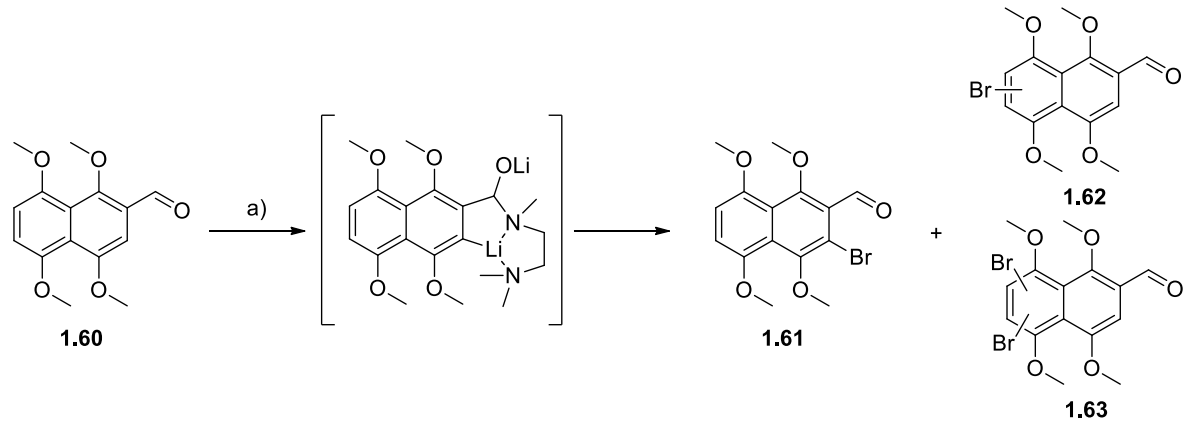
Hence, we turned to an electron rich aromatic moiety (**1.59**) with the structure and oxidation state of lomaiviticin and kinamycin in mind (Scheme 1-18). **1.59** was prepared previously[37] and also the subsequent Vilsmeier-Haack reaction to the corresponding aldehyde **1.60** was already reported.[38] It thus boded well for the scaffold and guaranteed a benzylic group.



Scheme 1-18 Building the new aromatic wing and introducing the benzylic carbon by Vilsmeier-Haack reaction. a) $(COCl)_2$, DMF, $CHCl_3$, 60°C, 88%.

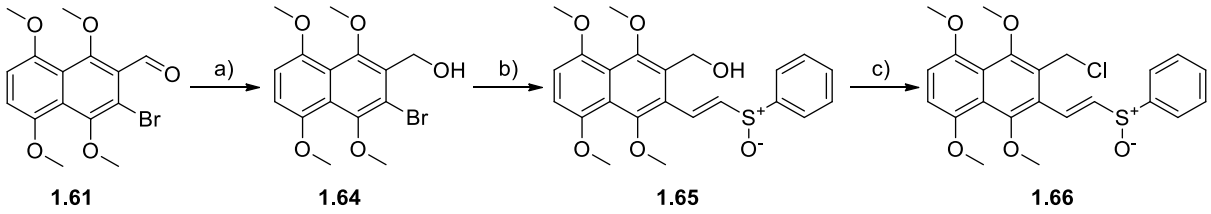
Aldehyde **1.60** was accessible in multi-gram quantities after little modifications of the conditions ($(COCl)_2$ instead of $POCl_3$) in excellent yield. The next step was to introduce the bromide *alpha* to the aldehyde, which was envisioned to be done by *ortho* lithiation and subsequent addition of an electrophilic bromine source. Therefore, **1.60** was treated with trimethyl ethylene diamine to give an *alpha* directing hemi aminalide. Upon treatment with *n*-BuLi and a subsequent quench with CBr_4, the desired *alpha* brominated product **1.61** was obtained as the major isomer, but in a cripplingly low yield of 17% (Scheme 1-19). Analyses of the reaction after CBr_4 addition by either ^{1}H NMR or UPLC-

MS suggested clean transformation to the two possible isomers **1.61**, **1.62** and double adduct **1.63** (**1.61** : **1.62** : **1.63** = 2 : 0.7 : 0.8) together with some leftover starting material **1.60**. It is thus not clear why such a low yield was obtained. Any attempts to optimize the yield by changing reagents, set-up or conditions failed.



Scheme 1-19 Bromination after *alpha* lithiation. a) $LiN(Me)CH_2CH_2N(Me)_2$, then *n*-BuLi, then CBr_4, toluene, 17%.

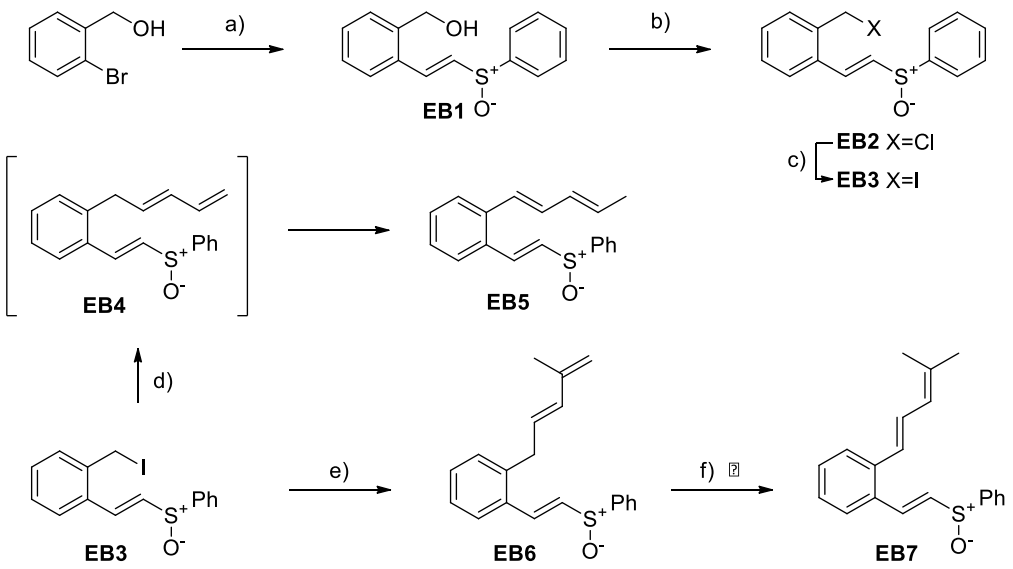
Nevertheless, the upcoming steps were approached. First, aldehyde **1.61** was reduced to the corresponding benzylic alcohol **1.64** (Scheme 1-20). This reduction happened without event and gave the desired product in good yields without further purification than extraction after workup. Subsequently, the benzylic alcohol was subjected to the sulfoxide Heck conditions. The desired cross coupled sulfoxide **1.65** was obtained in acceptable yield but lower than expected. **1.65** was subsequently transformed into its respective benzyl chloride **1.66** via a mesylate in a single step.



Scheme 1-20 Reduction, Heck reaction and chlorination. a) LAH, THF, 0°C -> rt, 88%; b) phenyl vinylsulfoxide, NEt_3, 20 mol% $Pd(PtBu_3)_2$, dioxane, 80°C, 54%; c) MsCl, DBU, DCM, 0°C -> rt, 52%.

The experimental base for the preparation of chloride **1.66** from alcohol **1.64** was investigated on a model system by Enrique Blanco in 2012 as a part of his master thesis under the supervision of the author of this thesis. Blanco successfully coupled a vinyl stannane with his aromatic model system and made the first attempts towards the Diels-Alder reaction (Scheme 1-21). Unfortunately he was not able to obtain the desired tricycle but observed an isomerization of the diene towards the

aromatic ring in two different cases (**EB5** and **EB7**), rendering the molecule useless for the synthesis of a lomaiviticin or kinamycin model system.

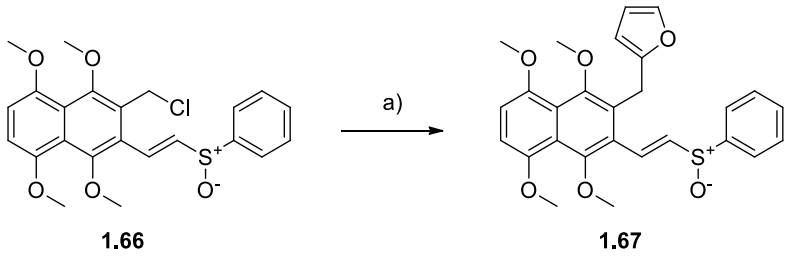


Scheme 1-21 Model system by Enrique Blanco which revealed that dienes tend to isomerize towards the aromat. a) phenyl vinylsulfoxide, NEt_3, 10 mol% $Pd(PtBu_3)_2$, dioxane, 80°C, 90%; b) MsCl, NEt_3, Et_2O, rt, 80%; c) NaI, acetone, rt, 86%; d) 1,3-butadiene tributylstannane, $Pd(PtBu_3)_2$, dioxane, 80°C, then 120°C in toluene; e) 3-methyl-1,3-butadiene boron pinacolester, $Pd(PPh_3)_4$, K_3PO_4, THF/H_2O, rt, 58%; f) various Lewis acids and heat.

These results found by Blanco were as frustrating as they were obvious and suggested that a synthesis of Lomaiviticin with our approach was unlikely to be possible. Interestingly, the methyl group introduced in **EB6** made the diene significantly more stable towards the isomerization compared to **EB5**, but couldn't prevent it. So it was still possible that maybe in the case of the more electron rich moiety **1.66** and with the ethyl groups in the tetraene (compare with **1.46)** the desired Diels-Alder would have happened according to the plan. Nevertheless, it was unlikely and we thus had to think of a possibility to fix the diene in its desired isomer.

The furan scaffold seemed a good choice. The diene was fixed and numerous examples of furans employed in Diels-Alder reactions were reported.[39] However, a furan would not have given entry towards lomaiviticin but kinamycin. We thus decided to pursue the synthesis of kinamycin and come back to lomaiviticin once more knowledge about the upcoming chemistry was gathered.

As the consequence, commercially available furanyl tributylstannane was cross coupled with benzyl chloride **1.66** and the desired furan **1.67** was obtained in mediocre yield.



1.66 **1.67**

Scheme 1-22 Stille coupling to give the model system for the intramolecular Diels-Alder reaction. a) furyl tributylstannane, 30 mol% Pd(P*t*Bu$_3$)$_2$, dioxane, 80°C, 31%.

Furan **1.67** allowed for the first time to test the Diels-Alder reaction and to evaluate if the sulfoxide is directing the face of cycloaddition as intended. Our predicted model towards the stereochemical outcome is shown in (Figure 1-7)

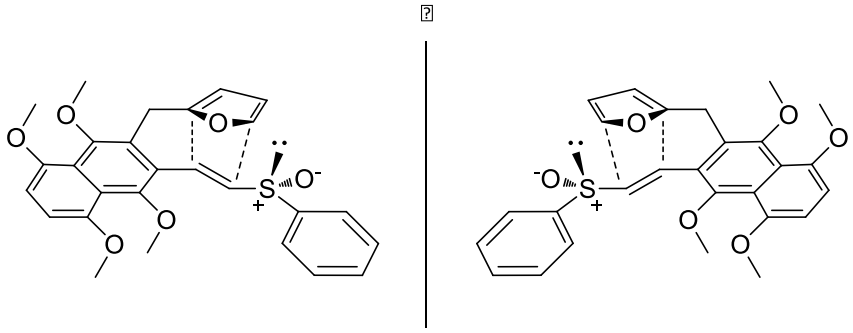
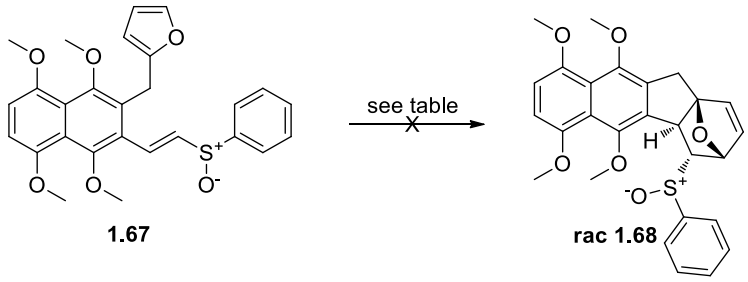


Figure 1-7 predicted transition state of the Diels Alder reaction, depending on the chirality of the employed sulfoxide.

Because only very small amounts of **1.67** over the last 5 steps starting from aldehyde **1.60** were obtained, not many Diels-Alder conditions could be probed. The results are showed in Table 1-7.

Table 1-7 Small reaction condition screening towards the Diels-Alder reaction.



Entry	Solvent	Additive	Temperature	Time	Outcome
1	toluene	-	130°C	15 h	No reaction
2	toluene	TMS-OTf	rt	0.5 h	Decomposotion
3	MeCN	TBS-OTf, 2,6-*t*Bu pyridine	-20°C -> rt	24 h	No reaction, then decomposition at rt

The first attempt towards **rac 1.68** was simple heating in toluene (Table 1-7, entry 1), which didn't lead to conversion but neither undesired decomposition was observed. Martin and coworkers published an informative study about furans undergoing Diels-Alder reaction with chiral vinyl sulfoxides.[40] According to their method, TMS-OTf was added (entry 2) to the toluene sample at room temperature, but the sample decomposed almost immediately. In a second attempt, **1.67** was treated exactly according to Martin (entry 3), which did not give any conversion at the reported lowered temperatures but decomposition was slowly observed at room temperature again.

1.3.6 Kinamycin – Kochi-Anderson reaction as a highly convergent tool

Since the Diels-Alder reaction was not working as intended, a more in-depth analysis of the system was done. Under consideration of electronic effects we concluded that the Diels-Alder reaction would be favored if the quinone were in its oxidized state and further accelerated if the methyl group on the furan were present as it is the case for kinamycin (Figure 1-8).

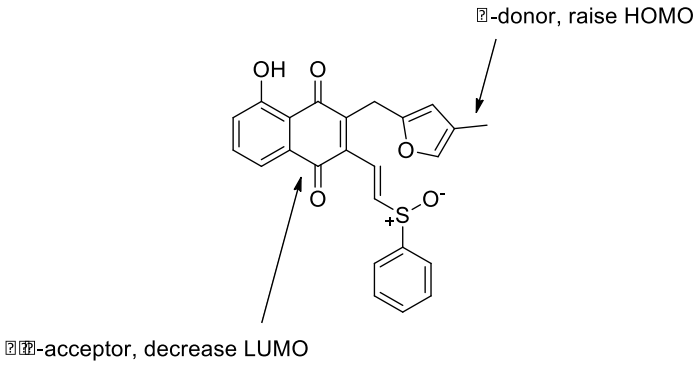
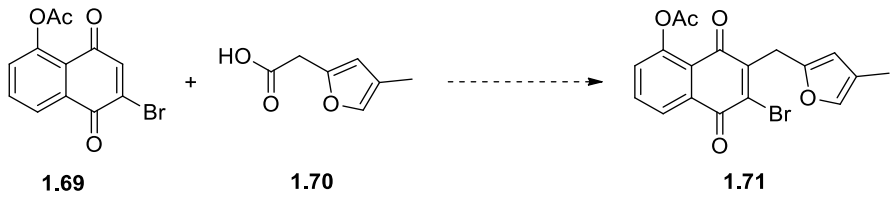


Figure 1-8 Analysis of the Diels-Alder reaction towards kinamyicn.

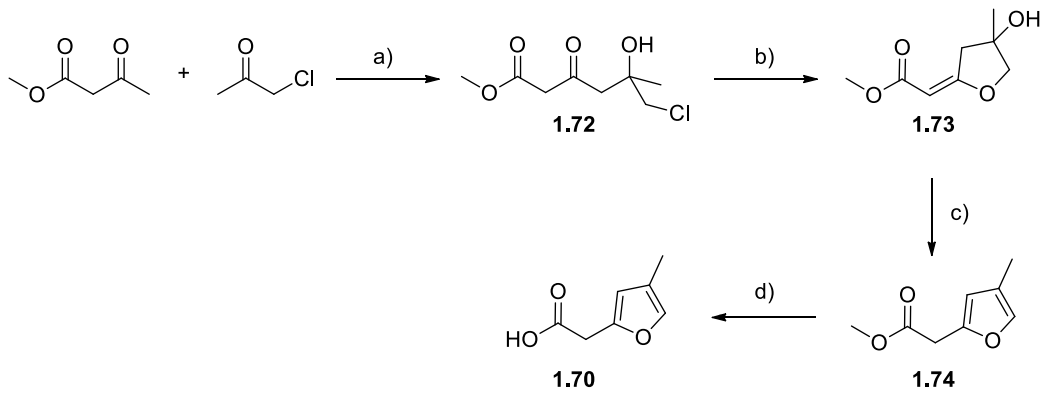
Since the low yield over the entire sequence was making an excessive screening of the Diels-Alder reaction impossible, we decided to leave the model system and establish a route to kinamycin. The major difference was the aromatic moiety with one oxygen less, being now asymmetric and thus impeding the selective additions to it.

As discussed we intended to perform the Diels-Alder reaction with a quinone instead of a hydroquinone (*vide supra*) and accordingly tried to avoid the protection / deprotection steps. Inspired by the work of Nicolaou[9], we envisioned a radical addition to the quinone, which in Nicolaou's case gave access to an allyl quinone. We wanted to add as much functionality as possible in this single step though and thus planned to attach the entire heterocycle **1.70** by a Kochi-Anderson reaction (Scheme 1-23).



Scheme 1-23 Envisioned 1,4-addition of a furan to the unprotected quinone.

Test reactions with quinone and commercial furan acetic acid were successful, hence the synthesis of furan **1.70** was approached (Scheme 1-24).

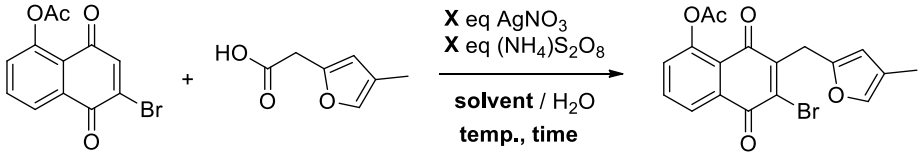


Scheme 1-24 Synthesis of methyl furan acetic acid 1.70: a) NaH, *n*-BuLi, THF, 0°C; b) DBU, DCM, rt; c) TFA, DCM, 0°C –> rt, 15% over 3 steps; d) LiOH, THF/H_2O, rt, 82%.

In the first step methyl acetoacetate was lithiated twice according to Huckin's[41] procedure and added to chloro acetone. On small scale full conversion was observed, but on a multi gram scale, this reaction turned out to be sluggish. In order to minimize labor, chloride **1.72** was cyclized without further purification to alcohol **1.73** by treatment with DBU. After an acidic wash to remove the amine base, crude **1.73** was treated with TFA which afforded the desired furan **1.74** after elimination of water and isomerization of the *exo* double bond. Ester **1.74** was purified by flash chromatography and was obtained in mediocre yield over three steps. The final hydrolysis with LiOH gave the desired furan acetic acid **1.70** in good yield on a 1 g scale.

Quinone **1.69** was made according to a literature procedure[42] and with access to furan **1.70** in good amounts the Kochi-Anderson coupling was attempted. Unfortunately, the conditions which were successfully employed in the test reaction of **1.69** with commercial furan acetic acid did not give the desired product **1.71** (Table 1-8, entry 1). The additional methyl group in **1.70** had such a big influence on the reaction that quinone **1.69** was mostly unchanged, furan **1.70** completely decomposed and a few new quinone-like peaks were observed in the ^{1}H NMR spectrum. A systematic screening had thus to be started.

Table 1-8 Kochi-Anderson reaction screening.



1.69 **1.70** **1.71**

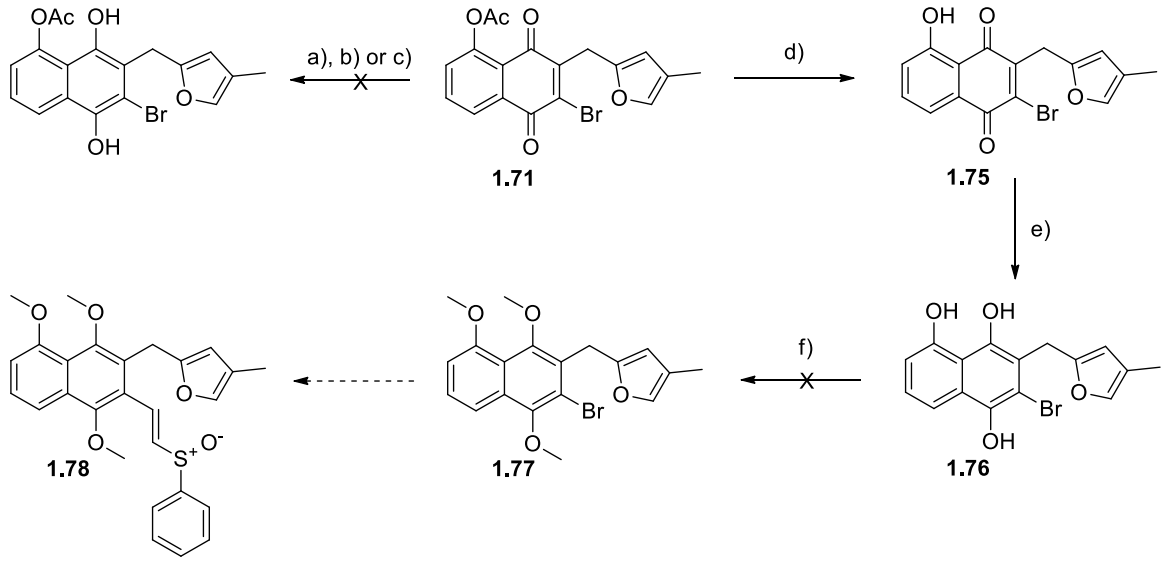
Ent.	$AgNO_3$	$(NH_4)_2S_2O_8$	Solvent	Temp.	Rxn. Time[a)]	Rate of add. $(NH_4)_2S_2O_8$ in H_2O	Outcome
1	0.3 eq.	2 eq	MeCN	65°C	4 h	Over 30 min	Quinone side product
2	0.3 eq	2 eq	TFT	rt	0.5 h	Over 20 min	Only **1.69** left
3	0.3 eq	2 eq	TFT	45°C	0.5 h	Over 20 min	Only **1.69** left
4	0.3 eq	2 eq	TFT	60°C	0.5 h	Over 20 min	Only **1.69** left
5	0.3 eq	2 eq	acetone	rt	0.5 h	Over 20 min	New product in small amounts[b)]
6	0.3 eq	2 eq	acetone	45°C	0.5 h	Over 20 min	New product in small amounts[b)]
7	0.3 eq	2 eq	acetone	60°C	0.5 h	Over 20 min	New product in small amounts[b)]
8	$Ag(pi)_2$[c)]	-	acetone	60°C	0.5 h	-	decomposition
9	2 eq	2 eq	acetone	45°C	0.5 h	Over 20 min	Complete decomp.
10	0.1 eq	2 eq	acetone	60°C	0.5 h	Over 20 min	Mainly decomp.
11	0.1 eq	2 eq	acetone	60°C	23 min	fast	Product-peaks vanish after 6 min
12	0.1 eq	3 eq	acetone	60°C	15 min	fast	Product stable up to 15 min
13	0.3 eq	5 eq	acetone	60°C	10 min	fast	50% conversion of **1.69**, no more **1.70**
14	0.3 eq	5 eq	acetone	60°C	10 min	fast	1.3 eq **1.70**: Full conversion

a) time including addition of persulfate, b) peaks vanished over the prolonged reaction time, c) Ag $(pi)_2$ = silver(II) bispicolinate.

The first change was trying different solvents and temperatures and the reactions were carefully monitored by measuring ^{1}H NMR aliquots. While the employment of α,α,α-trifluorotoluene (TFT) gave only quinone starting material **1.69** and furan **1.70** was completely gone at temperatures between rt and 60°C (entry 2-4), acetone gave the first promising peaks in the aliquot spectra. However, these peaks were marginal compared to others and they also vanished over prolonged reaction time (entry 5-7). At room temperature, hardly any new peaks were observed, at 45°C they were more pronounced and even better at 60°C, however at 60°C in acetone also more quinone sideproside productduct peaks were observed. It was not known yet what was prohibiting the conversion and as an alternative to *in situ* generated Ag(II), a stable source of Ag(II) was added as silver picolinate (entry 8). This reagent, however, did lead to complete decomposition of the quinone and the furan starting materials. The use of an excess of $AgNO_3$ led to complete decomposition as well (entry 9) and it seemed that silver had a bad influence on the desired reaction outcome. Trying to optimize into another direction, the amount of silver was lowered (entry 10) but still mostly decomposition was observed. Trying to understand what gave the new promising signals in in entries 5-7, the oxidant was added in one batch and aliquots were taken starting from minute 1 to minute 23 (entry 11). This experiment turned out to be very important in order to understand the reaction. It revealed that the desired product **1.71** formed within the first few minutes of the reaction and then from minute 6 it started to decompose again. Repeating the experiment with an excess of oxidant even allowed the product to be stable up to 15 minutes in solution at 60°C (entry 12). It was concluded that Ag(I) was likely the reason for decomposition of **1.71** and an excess of ammonium persulfate was allowing for a more efficient regeneration to Ag(II). Thus the slow addition of only 2 eq of persulfate in the initial experiments (entries 1-10) did not furnish product **1.71**, because probably not enough oxidation potential could be provided to keep the concentration of Ag(I) low. The overall conversion in entry 12 was still low though, hence more silver and even more oxidant was added (entry 13), which led to 50% conversion of quinone **1.69** within the first 10 minutes before decomposition was observed again. In order to push the reaction to full conversion, 1.3 eq of furan **1.70** was added (entry 14) and indeed full conversion of the quinone to the desired product was observed.

Under the conditions employed in entry 14, furano quinone **1.71** was obtained in 42% yield on a 40 mg scale. On a bigger scale (up to 1.2 g of **1.69**) no full conversion was observed anymore and since **1.69** coeluted with the desired product **1.71** under normal phase flash chromatography a second purification by preparative HPLC was necessary. Under these circumstances an average yield of only 15% was obtained, making the progression of the project cumbersome.

The subsequent Heck reaction was performed on the quinone but as expected it didn't give the desired product. A 1,4-additon of a vinyl sulfoxide would have been the ideal solution, however because the Heck methodology was already established and the reduction to hydroquinones with subsequent methylation was successfully performed in several cases before (*vide supra*) we turned to the reduction/protection scheme, although we initially wanted to circumvent it. Ironically, the reduction of furano quinone **1.71** with the otherwise so well working sodium dithionate reagent, gave nasty product mixtures (Scheme 1-25). $NaBH_4$ and Luche reduction performed similarly bad. After removal of the acetate to give phenol **1.75** in good yield, the reduction with dithionite performed smoothly, however the subsequent trimethylation of the air sensitive hydroquinone was not performing as intended either.



Scheme 1-25 Troublesome reduction and protection of the Kochi-Anderson product. a) $Na_2S_2O_4$, H_2O, Et_2O, EtOAc, rt b) $NaBH_4$, MeOH; c) $NaBH_4$, $CeCl_3$, THF, H_2O; d) LiOH, H_2O, THF, rt, 72%; e) $Na_2S_2O_4$, H_2O, Et_2O, EtOAc, rt, 65% conversion; f) K_2CO_3, Me_2SO_4, acetone, 70°C.

Because we had severe difficulties to obtain enough material for an in-depth screening of a selective re-protection of **1.75** or at least a trimethylation of the corresponding hydroquinone **1.76**, further optimization of the Kochi-Anderson reaction was desperately needed. Although many difficult problems were solved on the way towards a total synthesis of either kinamycin or lomaiviticin, our progress regarding making a natural product was small. No proof of concept for the key step Diels-Alder reaction was present which could have justified intense investigations on an earlier step.

We thus had to evaluate whether a continuation was still reasonable or if a resignation after 2.5 years without reaching the target was appropriate. For our group, kinamycin and lomaiviticin was interesting for several reasons: The synthesis of diazo bearing molecules, elucidation of the biosynthetic pathway of the diazo group and the investigation of the mode of action of its DNA damaging activity.

Over the time of our synthetic efforts towards kinamycin and lomaiviticin a synthesis of lomaiviticin was reported by Herzon[11] and optimized isolation techniques from fermentation broths, inlcuding isolation of new analogs were published.[43] Further, a detailed report about the DNA damaging activity of kinamycins and lomaiviticins was reported.[7,44] The only relevant open question for us remained the biosynthetic pathway of the diazo. This single task alone however, didn't justify the continuation of the synthesis in our opinion.

The decision to give up on the total synthesis of kinamycin and lomaiviticin was not easy but it seemed to be reasonable. In the perspective of a PhD student, the excitement of starting to work on the synthesis of locked nucleic acids (LNA, see chapter 2) was fortunately larger than the disappointment of turning the back to kinamycin and lomaiviticin.

1.4 Conclusion and perspective

Neither the total synthesis of kinamycin, nor the one of lomaiviticin could be completed. Nevertheless, during the intensive studies a lot of exciting chemistry was discovered and developed. Not only a general protocol for the Heck reaction with aryl vinyl sulfoxides was established, but it also was successfully expanded on sulfides and sulfones, later also on alkyl vinyl sulfides/sulfoxides/ sulfones. During the attempts of coupling two quinone flanks with the tetraene centerpart, we found ourselves strongly constrained due to the sulfoxide and its ambivalent character. The electrophilicity of the sulfoxide led to instant reactions with strong nucleophiles such as alkyl lithium and magnesium reagents. On the other hand, the viable Pd cross couplings were limited by the strong donating effect of the sulfoxides which restricted the pool of catalytic systems due to catalyst poisoning as it was already observed during the development of the sulfoxide Heck reaction. The allylic coupling turned out extremely difficult: under all conditions where the diallyl species underwent oxidative addition it simply decomposed. The resulting change to a benzylic halide on the quinone was a step in the right direction, because the oxidative addition is more facile and the intermediate Pd species more stable. For any future attempts, the benzylic coupling can be considered as the way to go. After changing

from the model system to the lomaiviticin system (Scheme 1-18) and later on to the kinamycin system (Scheme 1-23) we experienced progression towards the natural products, but both pathways were thwarted by a step with yields around 15% (synthesis of **1.61** and synthesis of **1.71**). Just two steps after those reactions, we ran out of material, making in depth studies of the frontier reactions impossible and thus stalling the project. Unfortunately both reactions were already extensively investigated (described in the case of **1.71**) but still no higher yields were obtained. Nevertheless, the Kochi-Anderson reaction to make **1.71** represents to our knowledge the first example of a heterocycle addition to a quinone by this type of reaction. To our knowledge, the most complex addition so far was performed with amino acids.[45] The Kochi-Anderson reaction remains confusing: Although the fundamental decomposition with Ag(I) was elucidated, the reason for the low yields remained hidden. Apparently still a lot of the employed material decomposed in a non ^{1}H NMR traceable way. The employment of different Ag(I) sources and also the variation of counter ions of the persulfate could be a step in the right direction. Concerning the unsuccessful Diels-Alder reaction, speculations about the negative results can only be discussed superficially, since not enough reactions were run for a detailed conclusion. According to models, the frontier orbitals of the diene and the dienophile can overlap without the need for additional strain. A little strain or torsion is always needed though, since a five-membered ring is supposed to form. As discussed earlier, it is likely that the electronic effects on the furan and the vinyl sulfoxide in **1.67** were not ideal. However, this will remain a hypothesis, as the electronically optimized system (Figure 1-8) has not been synthesized.

If this project will be continued, Kinamycin is within reach. However, optimization of the Kochi-Anderson reaction would be the key to ensure enough material for future studies. The trimethylation to give **1.77** should be a solvable task and the subsequent sulfoxide Heck is considered to run without complications. Also the oxidation of methyl hydroquinones by CAN in the presence of vinyl sulfoxides to their corresponding quinones was successful in the case of **1.27k** (not shown or discussed in this thesis). Therefore nothing should be in the way of testing the Diels-Alder reaction as long as enough material can be pulled through the synthesis sequence.

Regarding Lomaiviticin, it would take some risk to find whether the allylic tetraene isomerizes into conjugation with the aromatic flanks, rather than engage in a Diels-Alder reaction. It is advised to not test it on a model system because as discovered by Blanco, marginal changes had strong impact on the isomerization behavior.

2 A new entry towards a facile synthesis of LNA monomers

2.1 Introduction

2.1.1 Oligonucleotide modifications in antisense drugs: concept and Kynamro

Antisense drugging is a rather new concept of fighting diseases on an earlier level than possible with conventional small molecule therapies. Adapted and inspired by naturally occurring small interfering RNA, antisense drugs are employed to regulate gene functions on a posttranscriptional level. In other words: mRNA, coding for a disease-relevant protein, is inactivated by selective hybridization with a complementary oligonucleotide and thus, translation of the mRNA to the protein is prevented (Figure 2-1). Final cleavage by e.g. RNase H leads to the destruction of the information carrier.

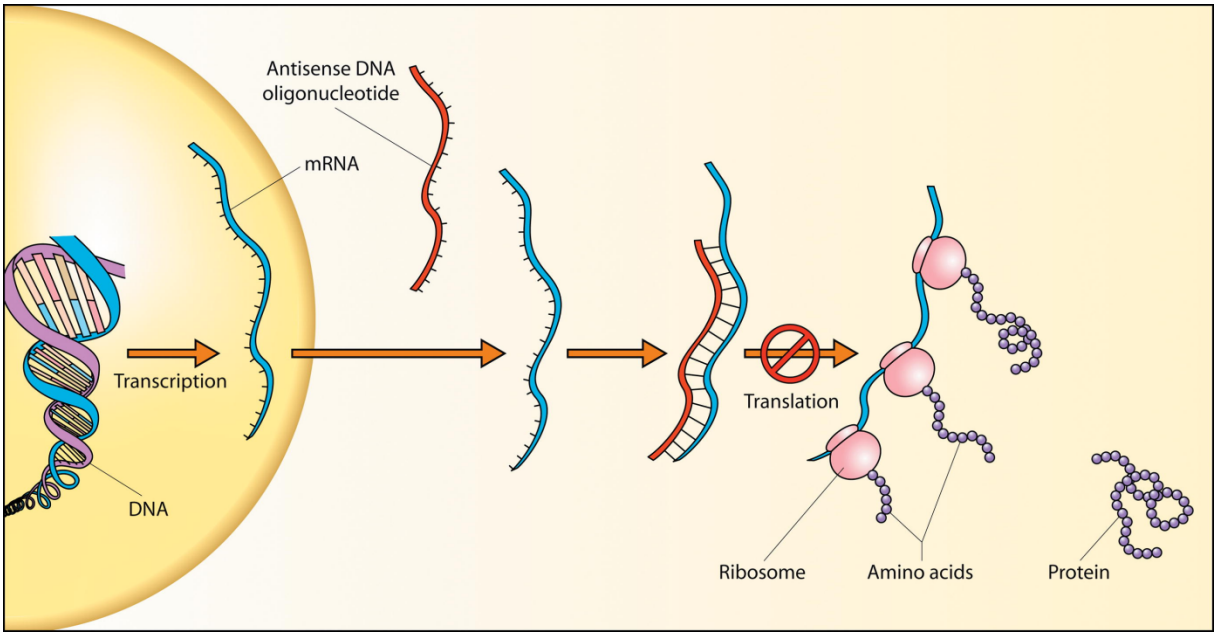


Figure 2-1 Schematic description of antisense hydridisation, preventing protein translation. With permission from: Robinson R (2004) RNAi Therapeutics: How Likely, How Soon? PLoS Biol 2(1): e28. doi:10.1371/journal.pbio.0020028.

The development of antisense drugs is still in its early stage and had its starting point in the early 1980's, rapidly emerging to become a hot topic in therapeutic development. Usually short oligonucleotide strands between 15 and 20 units are employed, which were found to be the optimal length for selective targeting and allow targeting diseases with a lot higher specificity than with conventional small molecules. Since different drug targets are only differentiated by the nucleobase code, standardized synthesis procedures are applicable for different targets, a welcome simplification given the unpredictability and complexity of small molecule synthesis.

One of the major hurdles currently limiting the application of antisense drugs is the delivery into cells. Because single stranded nucleic acids usually are indicative for a viral infection, single stranded antisense drugs are very quickly degraded in organisms and are repelled by cell membranes. These issues led to the development and introduction of modified backbones and furanoses. This concept was successfully applied in Kynamro, an FDA approved drug for treating homozygous familial hypercholesterolemia (Figure 2-2).

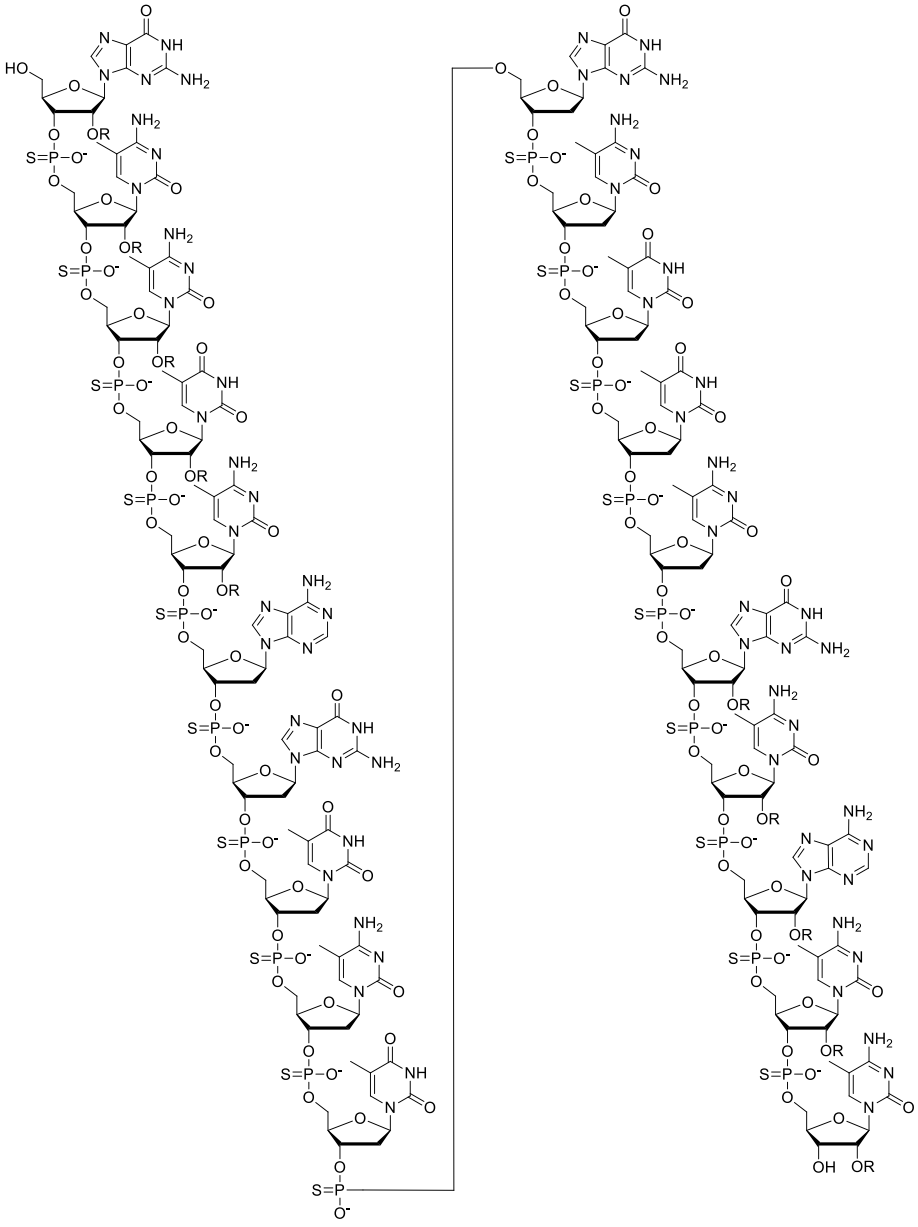


Figure 2-2 FDA approved antisense drug Kynamro by Isis pharmaceuticals:
5'-$G_m^{Me}C_m^{Me}C_m^{Me}U_m^{Me}C_mAGT^{Me}CTG^{Me}CTT^{Me}CG_m^{Me}C_mA_m^{Me}C_m^{Me}C_m$-3'; m = 2' modified with R; R = -CH_2CH_2OMe

A closer look on Kynamro reveals two modifications: a thiophosphate ester backbone modification and also a selective introduction of diethylene glycol methyl esters at the 3' position of the first and last 5 riboses. The backbone changes by thiolization are referred to 1^{st} generation modifications and introduce chirality. The S_p thiophosphate diastereomer was reported to have high stability towards nucleotide degradation but has a lower affinity towards binding target mRNA. On the other hand, the R_p thiophosphate diastereomer conferred high binding affinity but was found to be sensitive towards nucleases. Usually, diasteromeric mixtures are used as therapeutics and show attractive pharmacokinetic properties. The 2' ether modifications are referred to as the 2^{nd} generation of antisense oligonucleotides and add significant binding affinity and nuclease resistance, resulting in less side effects due to lower dosing of the drug. Nucleases recognize single stranded nucleotides by the free 2' hydroxyl, hence capping of these substantially reduces degradation in the cytoplasm. In the case of Kynamro, the introduction of 2' ether chains in the wings (first and last five furanoses) of the oligonucleotide reduced dosing from a daily to a weekly injection. The 3^{rd} and most current generation of antisense oligonucleotides contain modifications of the furanose ring. The most promising candidate in this generation is locked nucleic acid (LNA), which shows extraordinary thermal stability when hybridized to DNA, RNA or LNA, while maintaining nuclease resistance. A closer look at LNA is provided in 2.1.2. RNase activation is required for effective gene silencing, LNA-only oligonucleotides will not recruit RNAses because they resemble RNA/RNA duplexes, hence gapmers were developed. These multifunctional constructs contain wings of three to four nuclease resistant, strong binding LNA nucleotides flanking a gap of seven to ten thiophosphate (1^{st} gen.) modified DNA nucleotides. This combination allowed for stability in serum, while promoting selective and strong silencing of mRNA and activation of RNases.[46,47]

So far only two drugs were FDA approved, both coming from ISIS pharmaceuticals based in California. While the commercialization of the first was stopped due to shrinking markets, Kynamro is successfully marketed. The fact that so far only one drug is on the market containing only minor modifications of what is currently possible, reveals a lot about the current state of the art in this field. The complex synthesis of modified monomers is a big challenge: the introduction of enhanced hybridization and resistance against nucleases require tedious and laborious syntheses, hindering the development of these drugs on both scientific and commercial grounds.

It is thus the responsibility of organic chemists to develop syntheses to access engineered nucleotides in an economical manner to move antisense drugs from their infancy into an established future.

2.1.2 A closer look on 3rd generation modifications: Concept of fixed-pucker nucleic acids and structures published so far

The modifications of nucleotides reached its current 3rd generation where the furanose pucker is modified (see 2.1.1). The most prominent example is LNA (Figure 2-3) but many derivatives of its basic structure were developed which all possess the general property of a forced 3' endo pucker induced by an artificial strap between the 2' and 4' carbon (Figure 2-4).

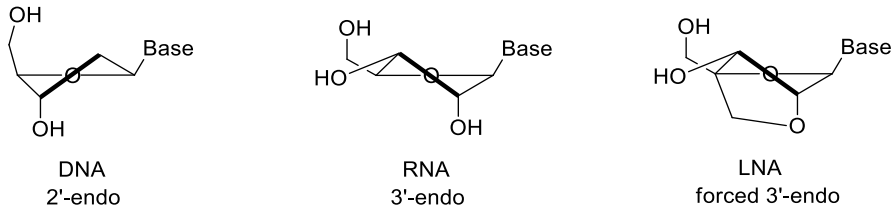


Figure 2-3 Conformations of pento furanoses in DNA, RNA and the forced pucker of LNA.

LNA was found after its first synthesis to exhibit an unprecedented strong binding affinity to DNA, RNA and LNA[48]. This phenomenon was attributed to a fixed pucker, which induced local organization of the phosphate backbone (entropic affect), in turn directing the strand into a conformation that favors a more efficient stacking in duplexes (enthalpic effect).[49]

To date numerous structures of LNA derivatives have been published and a selection is shown in Figure 2-4.

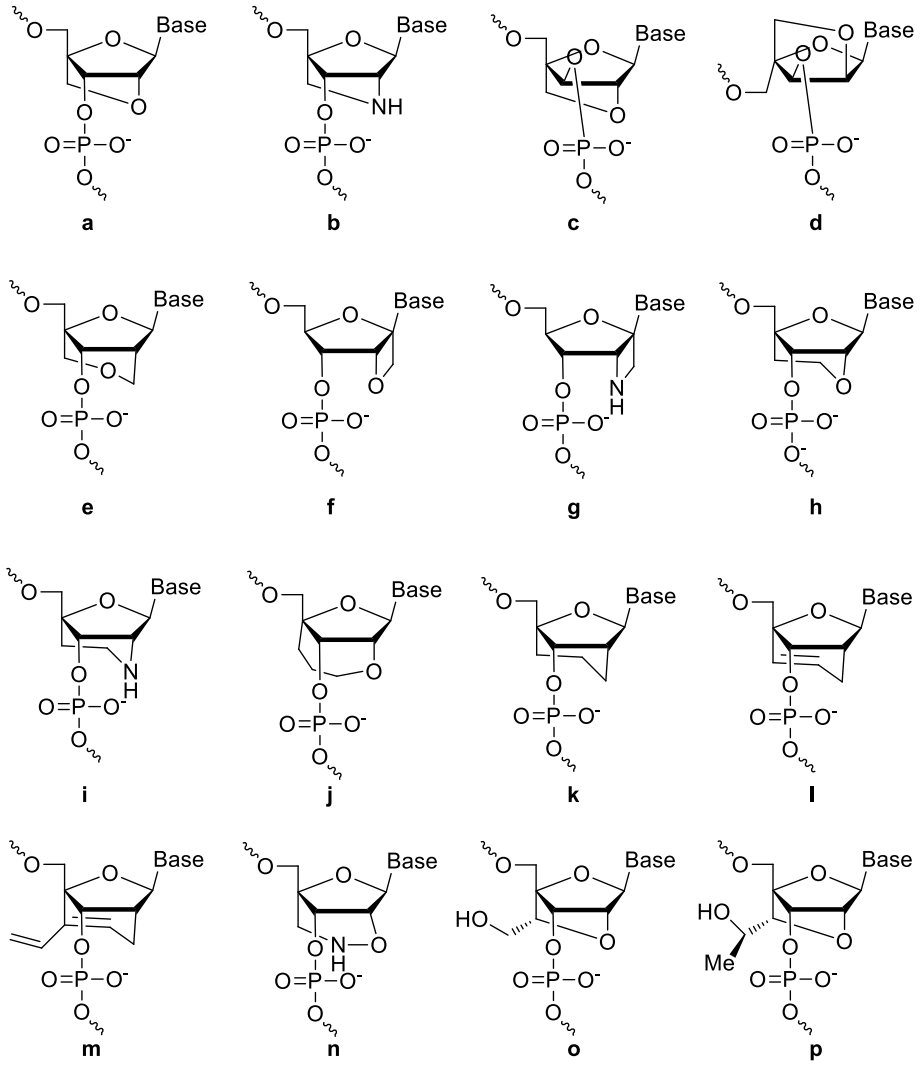
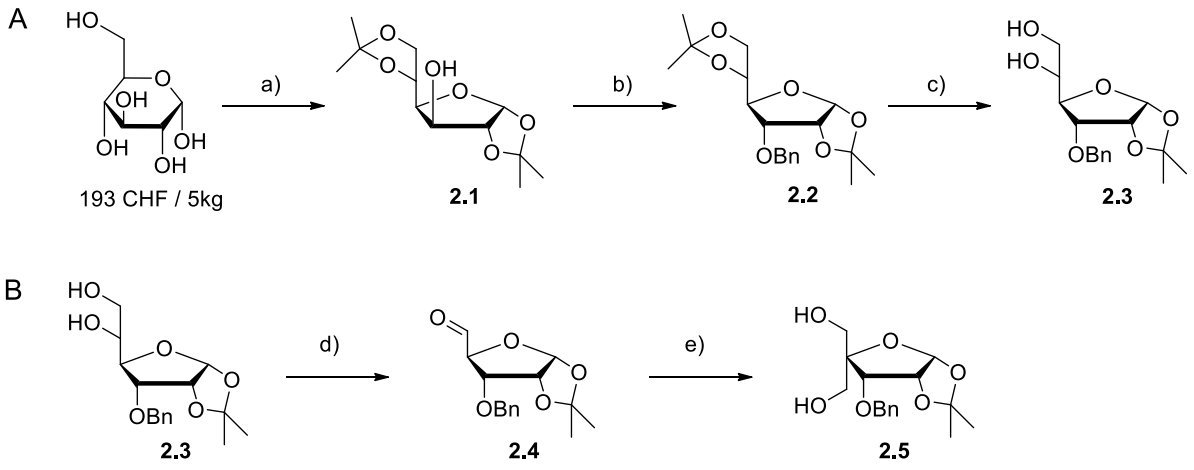


Figure 2-4 A selection of the most important locked nucleic acid analogs: a) LNA,[48] b) amino-LNA,[50] c) xylo-LNA,[51] d) α-L-LNA,[52] e) β-bicylonucleoside,[53] f) 1',2'-oxetane-bridged,[54] g) 1',2'-azetidine-bridged,[55] h) ENA,[56] i) aza-ENA,[57] j) PrNA,[56] k) saturated carbocyclic analogue of LNA,[58] l) saturated carbocyclic analogue of amino-LNA,[58] m) vinyl unsaturated carbocyclic analogue of LNA,[59] n) BNA^{NC},[60] o) CH2OH-BNA,[61] p) 2' O-Methoxyethyl LNA.[62]

2.1.3 Wengel's synthesis of LNA and Exiqon's optimization

It was in 1997 when Imanishi and coworkers published the first synthesis of a uracil LNA monomer.[63] This example certainly influenced Wengel's work and thus merits mention, but the synthesis itself is tedious, protecting group heavy and preparative details are missing. The actual synthesis will therefore not be discussed in here.

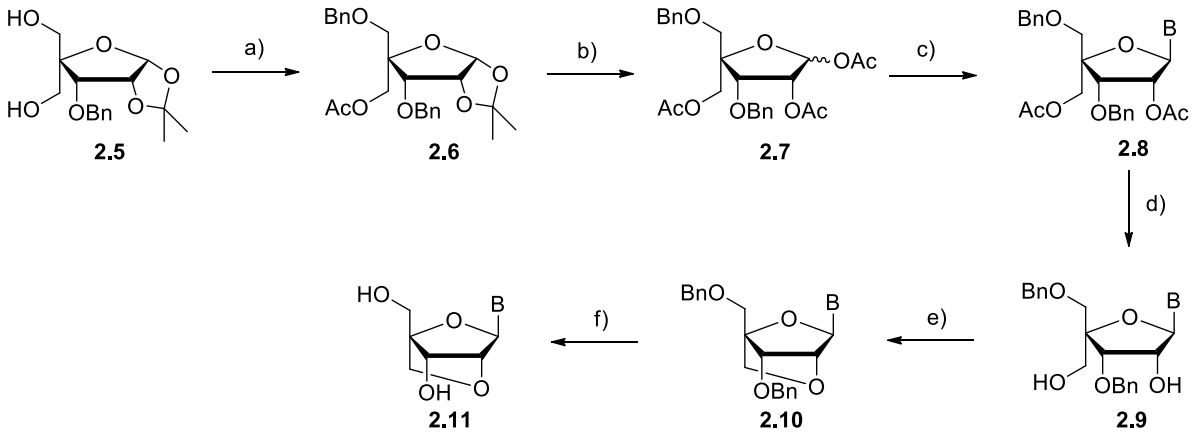
Wengel published in 1998 the first concise synthesis of LNA monomers with the canonical nucleobases A, T, G, C and U; He made the corresponding phosphoramidites and demonstrated their predicted potential in enhanced hybridization.[48] Wengel's synthesis is based on previously reported compound **2.5**, which can be made from cheap and bulk-available α-D-glucose.[64] α-D-glucose was first transformed by Fe^{3+} in acetone to its corresponding diacetonide **2.1**, which underwent oxidation of the 3' alcohol to the ketone. Diasteroselective reduction from the sterically less hindered top and subsequent benzylation gave furanose **2.2**. In the next step, selective acid hydrolysis gave access to the desired diol **2.3**. According to a procedure from 1979[65], diol **2.3** was first oxidatively cleaved to aldehyde **2.4**, which was subsequently enolized and added to formaldehyde to give 4' CH_2-OH modified furanose **2.5** serving as the basic starting material for all upcoming LNA syntheses by Wengel.



Scheme 2-1 Synthesis of the 4' CH_2-OH modified furanose 2.5. A[64]: a) $FeCl_3$, acetone, no yield given; b) 1) Swern, 2) $NaBH_4$, 3) BnCl, NaH, 79% over 3 steps; c) 80% AcOH aq, no yield given. B[65]: d) $NaIO_4$, quant.; e) H_2CO, NaOH, 67%.

It is important to mention at this point that the employed procedures towards **2.5** lack precise descriptions of the experimental details[65] and laborious reaction setups are required[64], nevertheless, since Wengel based his pioneering work (*vide infra*) on it, followed modifications, developments and iterations by other research groups were also based on **2.5** (see references Figure 2-4).

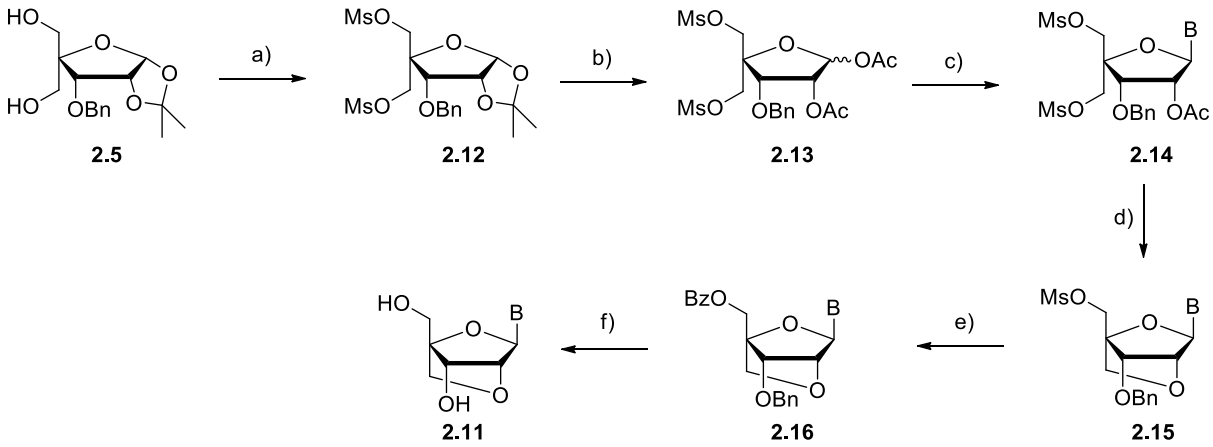
The 1st generation synthesis by Wengel[48] (Scheme 2-2) commenced with a selective 5' benzylation and subsequent acetylation to give furanose **2.6**. Then, the dimethyl ketal was cleaved under acidic conditions and the resulting diol was acetylated, yielding the precursor (**2.7**) for a diastereoselective nucleobase introduction. After successful silyl Hilbert-Johnson reaction (**2.8**), the acetates were hydrolyzed off under basic conditions (**2.9**) and the primary alcohol was tosylated which allowed for the subsequent ring closure to yield bicycle **2.10**. A final hydrogenation over $Pd(OH)_2$ on carbon gave desired LNA monomer **2.11**.



Scheme 2-2 First synthesis by Wengel: a) 1) NaH, BnBr, DMF, 2) Ac_2O, py; b) 1) 80% AcOH, 2) Ac_2O, py, 55% over 4 steps; c) nucleobase, BSA, TMS-OTf, MeCN, 76% for thymin; d) $NaOCH_3$, MeOH, 97%; e) 1) *p*TsCl, py, 2) NaH, DMF 42% over 2 steps; f) $Pd(OH)_2/C$, H_2, EtOH, 98%.

Neglecting the fact about the synthesis of starting material **2.5**, the procedure is straight forward and allows the preparation of LNA monomers without sophisticated techniques or dangerous reagents. However, the synthesis in Scheme 2-2 is arguably tedious and protecting group heavy, regarding the actual chemical transformations done on the sugar.

With this problem in mind and the requirement to produce monomers in big amounts a 2nd generation synthesis was reported by Exiqon[66] (Scheme 2-3).



Scheme 2-3 Second generation synthesis of LNA by Exiqon: a) MsCl, py; b) 1) 80% TFA, 2) Ac_2O, AcOH, 98% over 3 steps; c) nucleobase, BSA, TMS-OTf, MeCN, 88%; d) LiOH aq, THF, 94%; e) NaOBz, DMF, 86%; f) 1) NH_4OH, $MeNH_2$, MeOH, 78%, 2) $Pd(OH)_2/C$, HCO_2NH_4, MeOH, 83%.

The same starting material was employed, but instead of protecting diol **2.5**, it was found, that mesylated alcohols were stable enough to withstand the upcoming transformation and allow for the later ring closure without further activation. Hence, after mesylation (**2.12**), the dimethyl ketal was removed again under acidic conditions and the diol acetylated (**2.13**). An impressive yield of 98% over these three steps is reported. After nucleobase introduction under optimized conditions (**2.14**) a one-pot deacetylation and ring closure was performed, giving the desired bicycle **2.15** in a remarkable yield of 94%. Hydrolysis of the 5' mesylate in **2.15**, however, turned out to be not straight forward under aqueous conditions, therefore the mesylate was substituted to give benzoate **2.16**. After hydrolysis of the ester, transfer hydrogenation gave the final product **2.11** in an overall yield of 45% (for thymine).

The presented synthesis by Exiqon is a remarkable piece of work and allows the preparation of LNA with optimized yields. A big cut in protecting group chemistry was achieved by activating the alcohols on an early stage of the synthesis and using them as protecting groups. Concerning the chemistry shown in Scheme 2-3, only the substitution of the mesylate is not optimal and is thus adding an additional step to the sequence. Looking at the whole process though, reveals that an efficient synthesis is only possible if the diol **2.5** synthesis is excluded from the picture.

2.2 Retrosynthetic analysis

The shortcoming of Wengel's synthesis is the early stage, where the additional carbon at the 4'-position is introduced. We therefore envisioned a *de novo* synthesis from simple commercially available chemicals instead of brute force introduction of an additional carbon on the already existing scaffold. A further challenge we set, was to find a synthetic route which was as simple and cheap as possible. A practical synthesis for academic research should be userfriendly and allow the reproduction on a moderate scale without complex reaction setups or too hazardous reagents. Figure 2-5 shows the retrosynthetic analysis.

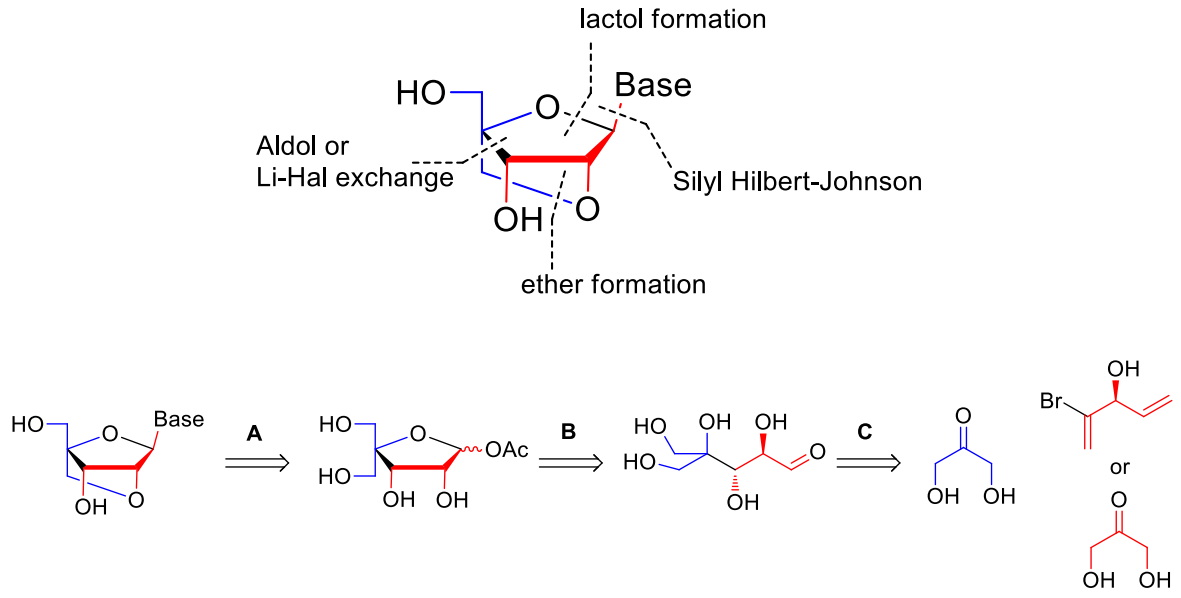


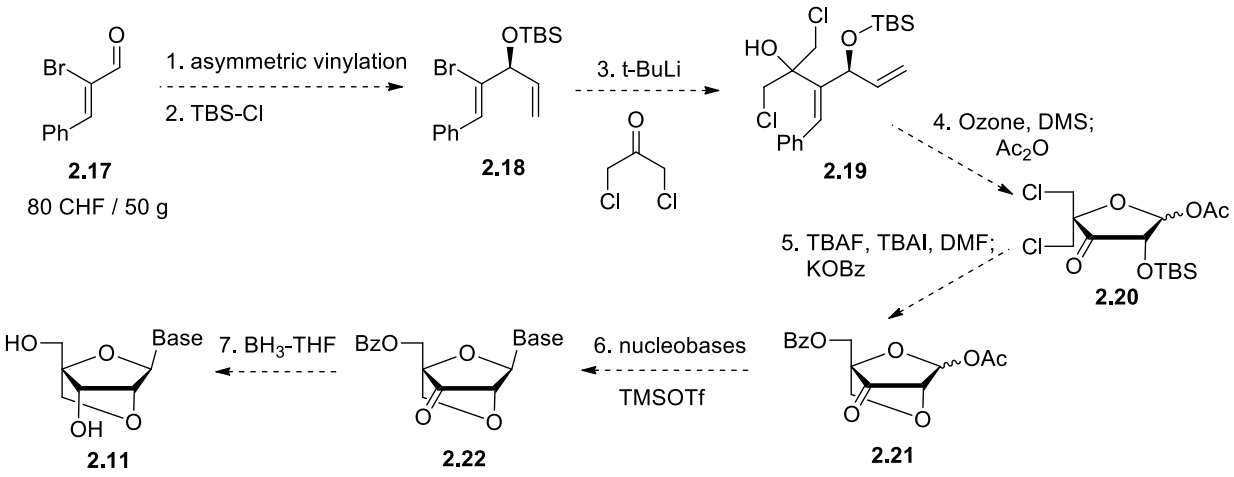
Figure 2-5 Retrosynthetic analysis of the LNA molecule. The two dihydroxyacetone scaffolds are marked in red and blue.

From a retro synthetic standpoint it was clear from prior art that the nucleobase should be added to a lactol by a silyl Hilbert-Johnson reaction (Vorbrüggen reaction, **A**), while stereochemical orientation of the alcohols at the 2'- and 3'-positions would direct stereocontrol to furnish the *anti* product. Forming the 2' - 4' bridge should be possible according to the displacement route developed by Wengel (**A**). Another rather obvious decision was the ring closure via lactol formation (**B**). The required anomeric aldehyde was envisioned to be introduced by either alcohol oxidation or ozonolysis of a terminal alkene; ring closure should follow spontaneously (**B**). On the other hand the initial scaffold synthesis by a formal aldol reaction of two formal dihydroxyacetone units is suspected to be the most challenging part of the synthesis (**C**). Chirality, the carbon frame and most of oxidation states will be introduced during the first few steps, which represent the innovative part of the synthesis.

2.3 Synthesis

2.3.1 1st generation synthesis: Li-Halogen exchange

The first generation synthesis plan is shown in Scheme 2-4.

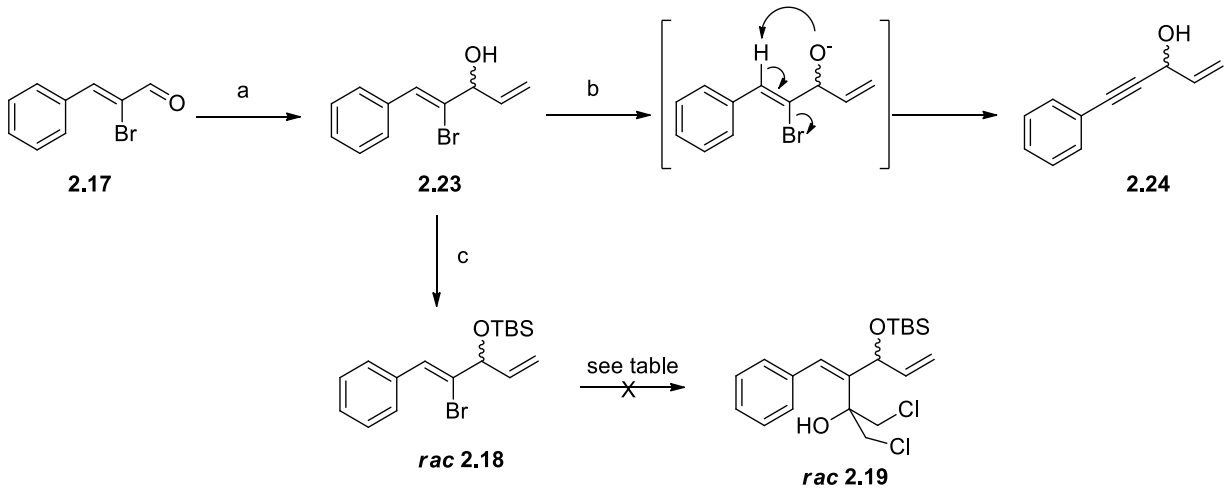


Scheme 2-4 1st generation synthesis plan towards a LNA monomer via lithium halogen exchange.

We planned to start with cheap commercially availbale 2-bromo cinnamaldehyde (**2.17**), vinylate and TBS-protect the formed alcohol to give **2.18**. Upon Li-halogen exchange and addition to dichloroacetone lelading to **2.19**, the two double bonds were envisioned to be oxidatively cleaved by ozonolysis to give a lactol, which could be acetylated *in situ* (**2.20**). The reactive hydroxyl, formed after TBS removal would cyclize and the second chloride was planned to be displaced by potassium benzoate (**2.21**). Subsequent introduction of the nucleobase (**2.22**) and final diastereoselective reduction would yield the desired diol **2.11**.

We started the synthesis as planned with the vinylation of 2-bromo cinnamaldehyde **2.17**, although in non-stereocontrolled fashion. Enantioselective vinylation of aldehydes have been reported[67-69] and were planned to be employed after a racemic synthesis was completed. We were pleased to find that the desired product **2.23** formed in 83% yield on a 1 g scale (Scheme 2-5).

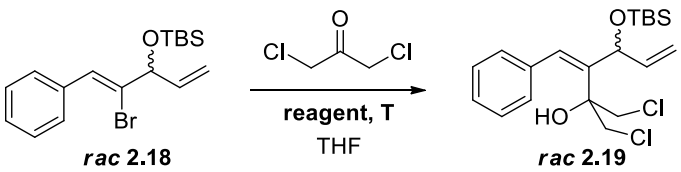
The subsequent deprotonation, Li-halogen exchange and addition to dichloroacetone was attempted with the free hydroxy group in **2.23** but unfortunately the only product isolated was the corresponding alkyne **2.24** which likely resulted from an intramolecular elimination after the alcohol deprotonation.



Scheme 2-5 Vinyl addition and attempted Li-halogen exchange: a) CH_2CH-MgBr, THF, rt, 83%; b) MeMgCl, *i*-PrMgCl LiCl, $ClCH_2COCH_2Cl$, 0°C –> rt; c) TBS-Cl, imidazole, DMF, rt, 86%.

As a consequence, alcohol **2.23** was TBS protected (***rac* 2.18**) and then subjected to Li-halogen exchange again. However, the bromide turned out to be very resilient towards the applied conditions and under most conditions (Table 2-1, entry 1-3) not even conversion to the dehalogenated product was observed.

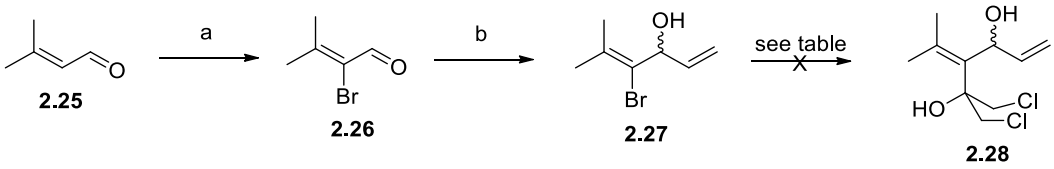
Table 2-1 Attempts of Li-halogen exchange on TBS protected alcohol *rac* 2.18.



Entry	Reagent	Temperature [°C]	Conv. of ***rac* 2.18**	Isolated ***rac* 2.19**
1	*i*PrMgCl LiCl	rt -> 60	-	-
2	Mg turnings	65	-	-
3	*n*-BuLi	-78	-	-
4	*n*-BuLi	-15	75%	complex mixture
5	*t*-BuLi	-78	60%	Complex mixture

Only under harsher conditions (entry 4-5) conversion was observed but no desired product ***rac* 2.19** was isolated.

Because the elimination of the bromide in **2.23** turned out to be troublesome and the TBS-protected moiety ***rac* 2.18** didn't undergo a smooth bromide exchange, the substrate was changed. 3,3-dimethylacrolein (**2.25**) was chosen as a substitute because there is no proton adjacent to lead to a bromide elimination and its availability in large quantities for a reasonable price. The bromination and subsequent elimation to afford the brominated moiety **2.26** was performed without event. The following vinyl addition also gave the desired allylic alcohol **2.27**, however in moderate yield only (Scheme 2-6).

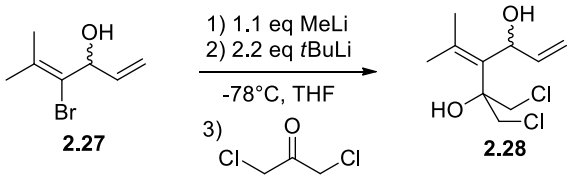


2.25 **2.26** **2.27** **2.28**

Scheme 2-6 Synthesis of alcohol 2.27: a) Br_2, NEt_3, DCM, 0°C -> rt, 99%; b) CH_2CH-MgBr, rt, THF, 44%.

With the new substrate **2.27** in hand, another round of Li-halogen exchange was started. The lithiation turned out to be fairly straight forward, but for unknown reasons the addition to dichloroacetone was not (Table 2-2).

Table 2-2 Attempts towards the addition of dichloroacetone after Li-halogen exchange.

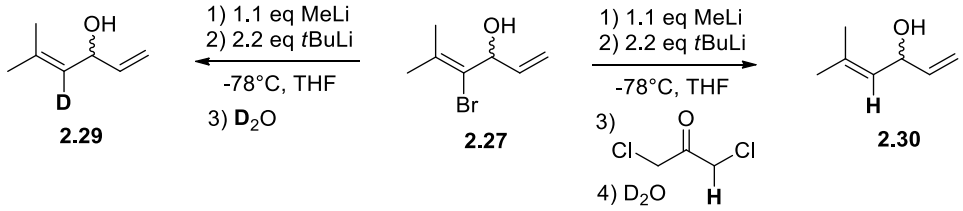


2.27 **2.28**

Temperature

Entry	T ketone addition	remark	Li-Br exchange	Yield of X
1	-78°C	Ketone added as a solid	ok	-
2	-78°C	Lithiated X added to a solution of ketone	ok	-
3	0°C	ketone added as solution in THF	ok	-
4	0°C	***i*PrMgCl LiCl**, ketone added as solution in THF	ok	-
5	rt	2eq $MgCl_2$, ketone added as solution in THF	ok	-
6	rt	2 eq LiCl, ketone added as solution in THF	ok	-
7	rt	2 eq $CeCl_3$, ketone added as solution in THF	ok	-

Addition of organo lithium[70] or magnesium[71] reagents to dichloroacetone have been reported and were reproducible in our hands. Change of temperature, inverse addition, and also common additives did not change the outcome of the reaction. Further, the quality of the dichloroacetone was assured by recrystallization prior to use[70] and it was thus not clear where the quenching proton was coming from. Eventually, a deuteration experiment revealed the reason for the difficulty (Scheme 2-7).

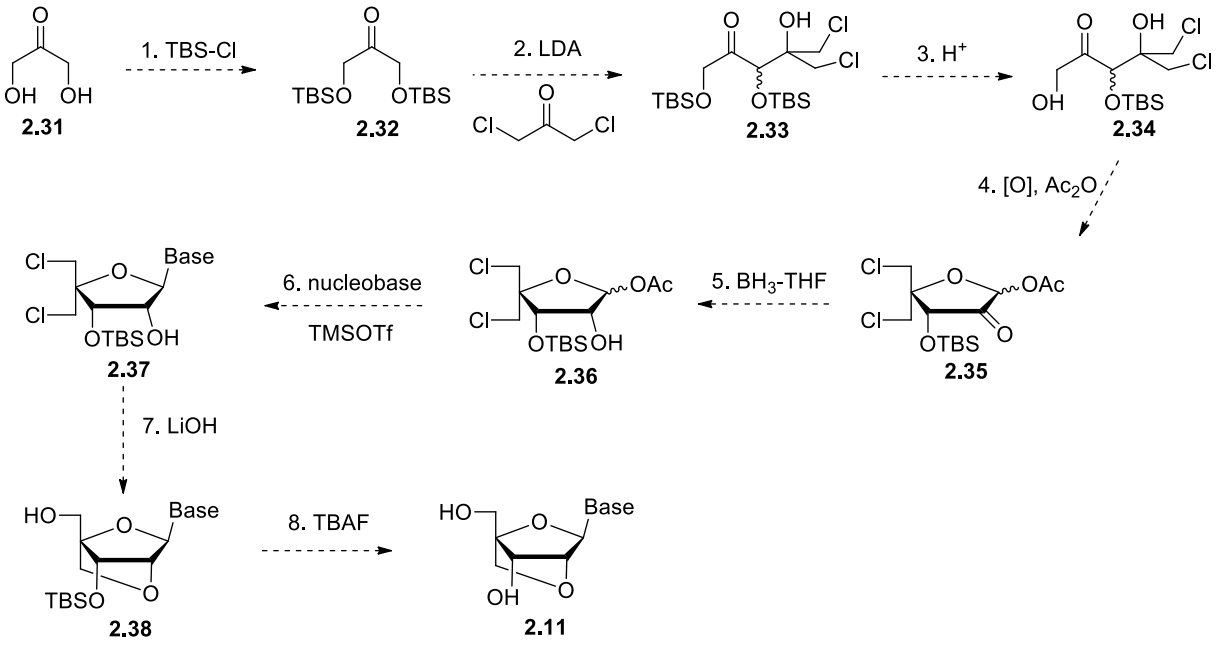


Scheme 2-7 Deuteration experiment shows that a deprotonation is favored over ketone addition.

If after deprotonation and lithiation of **2.27** an excess of D_2O was added, deuterated moiety **2.29** was obtained as a single product, showing that the lithium halogen exchange took place and the resulting nucleophile is able to add to an electrophile without being quenched by impurities in the reaction mixture. However, if dichloroacetone was added, followed by later addition of D_2O, exclusively protonated species **2.30** was obtained, indicating that the proton transfer was coming from the acetone. We thus concluded that probably the steric environment of lithiated bromide **2.27** prevented an addition to the ketone, hence only a more facile deprotonation on the activated alpha-carbon of the ketone occurred.

2.3.2 2nd generation synthesis: aldol reaction

Since alcohol **2.27** did not add to dichloroacetone, it was decided to attempt the connection by aldol chemistry. The synthetic plan is shown in Scheme 2-8.

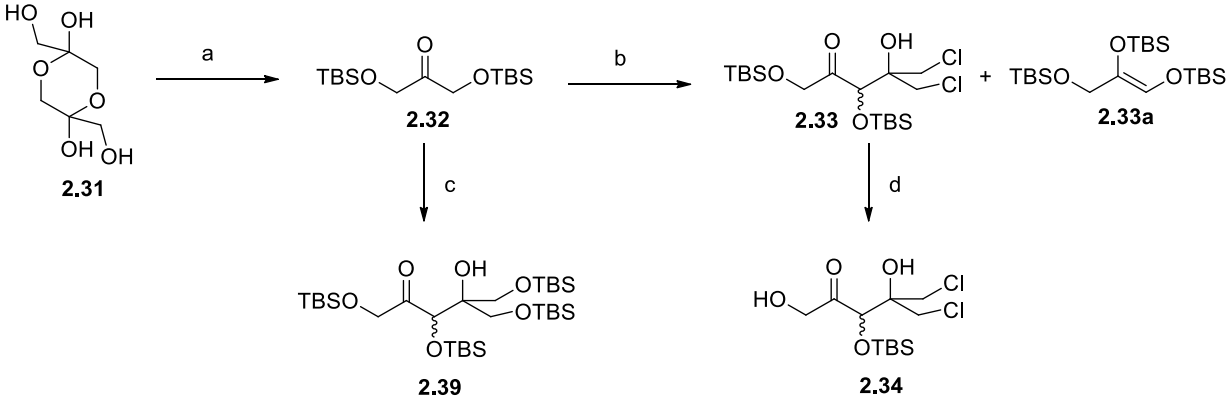


Scheme 2-8 2nd generation synthesis plan towards the LNA monomer via aldol reaction.

The plan of the 2nd generation synthesis was to first protect dihydroxyacetone with TBS (**2.32**) and then use its enolate to add in an aldol reaction to dichloroacetone to give the tertiary alcohol **2.33**. The formed stereocenter was planned to be controlled by a chiral organocatalyst or if troublesome, separation of the racemic mixture by acetylation of the formed alcohol and employment of a pig liver esterase in a chiral resolution[72]. After selective primary alcohol deprotection (**2.34**), oxidation to the aldehyde and spontaneous cyclization (**2.35**), we envisioned a diastereoselective reduction of the ketone to alcohol **2.36**. After silyl Hilbert-Johnson reaction to yield **2.37**, it would be activated in the next step to cyclize to the locked structure **2.38** by displacement of a chloride. In an optimal case, LiOH could be used for the cyclization and the hydrolysis of the second chloride. A final TBS removal would furnish the desired LNA monomer **2.11**.

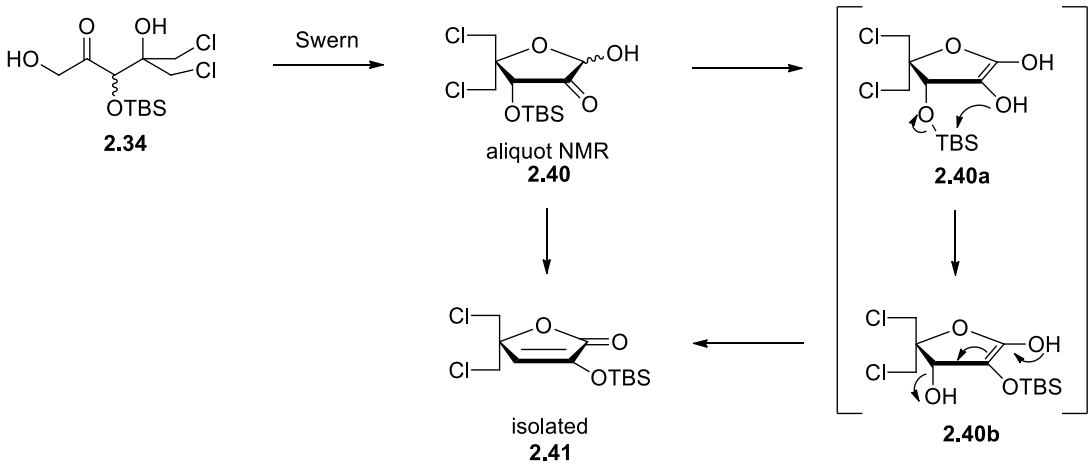
The TBS protection was reported[73] and allowed the synthesis of large amounts of **2.32** without event. The subsequent ketone-ketone aldol reaction came with the first problems to solve (Scheme 2-9). Although the reaction control looked positive at first glance, the formed product turned out to be homo coupled alcohol **2.39**. After reconsidering the sequence of reagent addition we were pleased to obtain the desired adduct **2.33** in moderate yield. Until to date no higher yield than 49% (1 g scale)

was obtained, but since the reaction could be run on a 7.4 g scale it provided enough material for the upcoming steps. One of the reasons for the rather low yield was the formation of enol ether **2.33a**, which resulted from a TBS swap instead of a ketone addition. The primary TBS group was then removed with aqueous acetic acid to afford alcohol **2.34** in good yields.



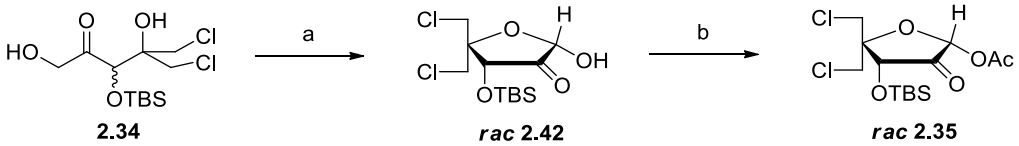
Scheme 2-9 Open chained sugar surrogate synthesis: a) TBS-Cl, imidazole, DMF, quant.; b) LDA, addition of 2.32 over 2h, $ClCH_2COCH_2Cl$, -78°C, THF, 35-49%; c) LDA, quick addition of 2.32, $ClCH_2COCH_2Cl$, -78°C, THF; d) 3:1:1 AcOH:H_2O:THF, 45°C 3h, 74%.

The next task was to oxidize alcohol **2.34** to an aldehyde. While reagents as DMP or IBX are very convenient, we were afraid of over oxidation to the lactone. Since the Swern oxidation only yields the oxidation product after decomposition of the reaction intermediates it was chosen for the next step (Scheme 2-10). The first few attempts were not successful and it was found that freshly distilled reagents were an absolute requirement for the transformation. Indeed after doing so, reaction mixture analysis suggested the transformation to a ring system and the characteristic anomeric proton signal was observed. However, upon workup and purification by flash chromatography a completely new species (**2.41**) was obtained.



Scheme 2-10 Successful oxidation and ring closure with unprecedented rearrangement during isolation.

It is suggested that the desired product **2.40** enolized to **2.40a**, swapped the TBS to the now more electron rich enol **2.40b** and then eliminated water in order to become the thermodynamically more stable dihydro lactone **2.41** during isolation. It was suspected that byproducts in the reaction mixture would lead to the enolization and thus a milder reagent was needed. After an intensive literature search we turned our attention to IBX, although we were skeptical about its usefulness in the beginning (*vide supra*). Corey reported the use of IBX in the oxidation of 1,4 diols to lactols[74] and we were very pleased to find that also in our case the desired lactol ***rac* 2.42** formed cleanly (Scheme 2-11). Interestingly, the reaction proceeded in a diastero selective manner and reaction control revealed a single diasteromer which was characterized by NOESY NMR spectroscopy as the *syn* product. After isolation a *syn* : *anti* ratio of 2:1 was usually observed, which likely formed due to water addition, ring opening and closing during work up. It is noteworthy that lactol ***rac* 2.42** was discovered to be not suitable for chromatography at all but being completely soluble in pentane and thus extraction from an aqueous DMSO solution allowed for isolation without chromatography, facilitating the process of ***rac* 2.42** in bigger quantities. However, byproduct formation on scale became an issue.

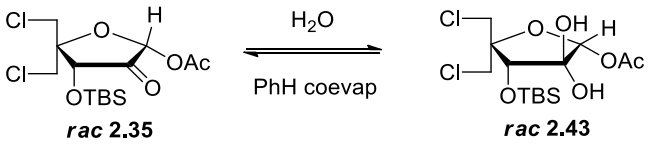


2.34 ***rac* 2.42** ***rac* 2.35**

Scheme 2-11 Oxidation and spontaneous ringclosure followed by acetylation: a) IBX, 40°C, DMSO; b) Ac_2O, rt, THF, 28% over 2 steps.

The reduction of the ketone was attempted with the obtained lactol because of the following acetylation: an acetylation of two hydroxyl groups at the same time seemed an obviously better choice than two subsequent single additions. But the result was a complex mixture and no reasonable reduction products were isolated.

rac* 2.42** was thus acetylated first in decent yield to give ***rac* 2.35** as single diastereomer, which worked efficiently on small scale. On a 1 g scale though, unremovable byproducts emerging from the oxidation complicated the process. Thus, purification by Preparative HPLC was necessary but several issues were faced: very low UV absorption even at 194 nm and elution over several inconsecutive fractions. Careful analysis of all fractions revealed the retention time and an unprecedented hydrate (rac* 2.43**) formation on the column in aqueous media which was stable upon lyophilization (Scheme 2-12).

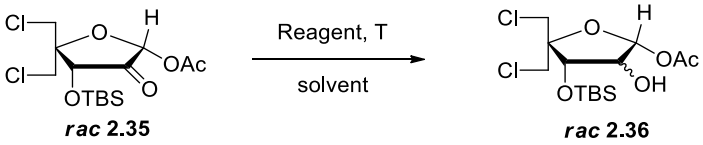


Scheme 2-12 Formation of an unprecedented stable hydrate.

Further purifications by preparative HPLC were thus performed with water pre-treated ***rac* 2.35** and applied as hydrate ***rac* 2.43**. This measure increased the isolated yield after HPLC by a factor of 14, but 28% over two steps were was still unsatisfactory. After isolation, hydrate ***rac* 2.43** could be reverted into the ketone by azeotropic codistillation with benzene.

The following reduction to alcohol ***rac* 2.36** initially proofed difficult (Table 2-3). With $NaBH_4$ depending on the solvent either a very complex mixture including loss of acetates and over reduction (Table 2-3, entry 1), or no conversion at all was observed (Table 2-3, entry 2).

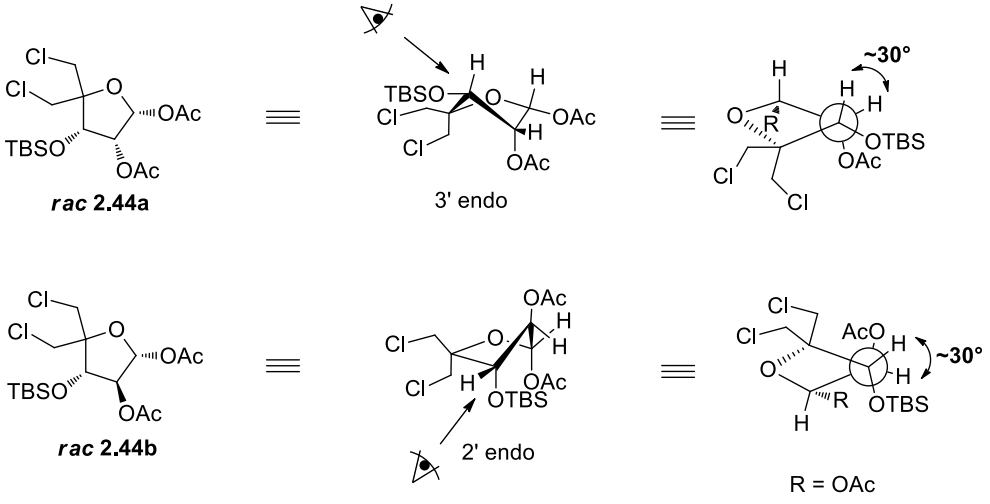
Table 2-3 Screening conditions towards the diastereo selective reduction of ketone 2.35.



Entry	Reagent	Temperature	Solvent	Conv.	Outcome
1	$NaBH_4$	rt	DCM/MeOH	99%	Over reduction, acetate reduction
2	$NaBH_4$	rt	AcOH	0%	No reaction
3	BH_3 THF	rt	THF	99%	Complex mixture
4	BH_3 THF	0°C	THF	99%	Complex mixture, acetate swap
5	BH_3 THF	0°C	Et_2O	99%	Single product

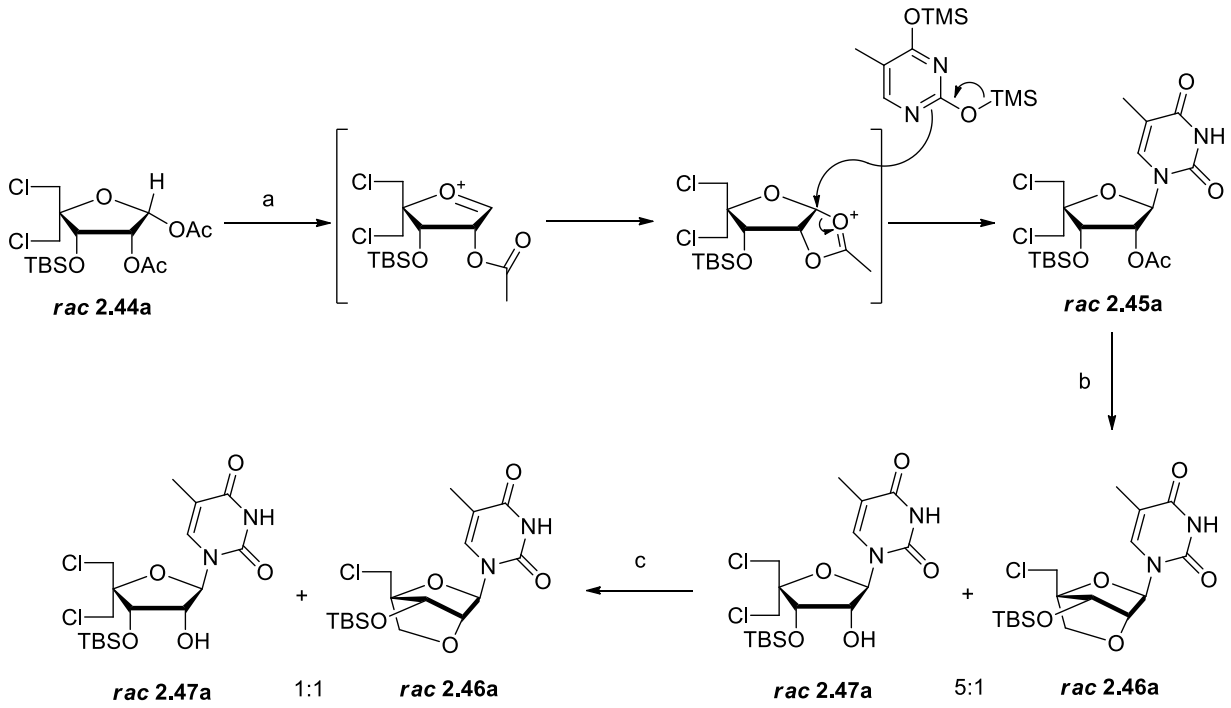
Borane-THF complex gave similar results (entry 3) but when the temperature was lowered, at least some products of the mixture could be isolated and it was concluded that upon reduction the acetate swapped positions (entry 4). Changing to less polar diethyl ether was a lucky decision and furnished according to crude NMR analysis a single product (entry 5). Unfortunately, isolation of this product (***rac* 2.36**) failed.

We thus acetylated the obtained alcohol ***rac* 2.35** directly after reduction, nevertheless a poor yield of diacetate ***rac* 2.44** was still obtained. The reduction gave clean aliquot crude NMR spectra consistent with product, hence it can only be speculated about the bad yield. Furthermore, no conclusion about the stereo chemical outcome was possible yet: depending on the ring pucker, the measured J-value between the 2' and 3' proton of 7.4 Hz could be explained for both possible diastereomers. In case of a 3' endo pucker the desired *syn* reduction (***rac* 2.44a**) would have occurred and in case of 2' endo pucker, the coupling constant would suggest to the undesired *anti* product (***rac* 2.44b**) (Scheme 2-13). Since in RNA a 3' endo structure usually is preferred[48] we were optimistic that we had the right molecule in hand.



Scheme 2-13 The stereo chemical outcome could not be determined since the arrangement of the ring pucker was not known.

Nevertheless, it was possible to synthesize enough material of ***rac* 2.44** to continue the study. Thymine was added to the furanose by a silyl Hilbert-Johnson reaction (Scheme 2-14). Diastereoselectivity was induced by the proximity effect of the 2' acetate. Upon elimination of the anomeric acetate, the 2' acetate added to the resulting oxonium ion, delivering a highly reactive cyclic oxonium. The subsequent attack of the silylated thymine occurred from the sterically more accessible exo face to give ***rac* 2.45a** or ***rac* 2.45b** (only desired product ***rac* 2.44a** is shown) in a diastereomeric ratio of 10:1 and in an excellent yield of 93%.



Scheme 2-14 Silyl Hilbert-Johnson reaction with furanose 2.44 and subsequent ring closure: a) BSA, TMS-OTf, Thymine, MeCN, 80°C, 93%; b) NaOH, rt, Dioxane, H_2O; c) NaI, DBU, DMSO, 90°C, 19%.

After nucleobase introduction the ring closure was attempted. According to Wengel's procedure[66] acetate ***rac* 2.45** was treated with LiOH in order to hydrolyse the ester and subsequently displace the adjacent chloride. In our case though, the formation of mostly free alcohol ***rac* 2.47** was observed and only minor amounts of the desired ring closure product ***rac* 2.46**. Hence, after some probing, it was found that with the help of NaI and DBU in DMSO the ring closure could be forced to proceed, although not to complete conversion.

With the introduced tether in ***rac* 2.46**, we put the ring pucker in a completely defined and non-flexible system, which now allowed the determination of the stereo chemistry, which was introduced during the ketone reduction. Very much to our disappointment and against the expectation (*vide supra*), NOESY NMR analysis of isolated bicycle ***rac* 2.46** strongly indicated the formation of the undesired *anti* product ***rac* 2.46b**. The important NOESY contacts are shown in Figure 2-6.

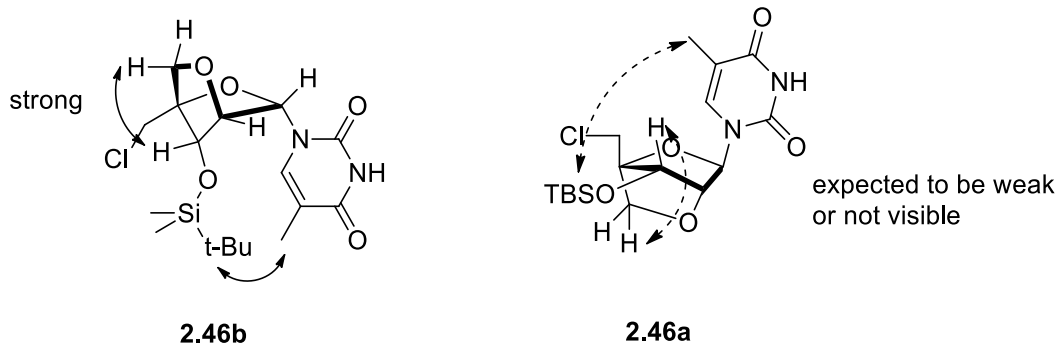
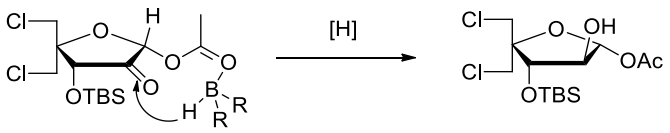


Figure 2-6 Observed (left) and expected (right) NOESY contacts of 2.46 suggesting the undesired product forming during reduction of ketone 2.35.

After the NMR analysis of ***rac* 2.46b** it was apparently necessary to go a few steps back in order to reevaluate conditions for the reduction of ***rac* 2.35**, giving access to the desired *syn* product ***rac* 2.46a**. Reduction of ***rac* 2.35** with DIBAL-H failed, giving the wrong diasteromer exclusively. L-selectride gave an ugly mixture of known and new unknown products, giving the possibility to have at least partially the desired diastereomer. Separation, however, proofed problematic and thus the mixture was subjected to silyl Hilbert-Johnson reaction in the hope to obtain a new product among the known ones (***rac* 2.45ab**), to no avail. We can only speculate why the expected *syn* product didn't form: one possibility is that the TBS group is so large that it does not just determine the face of addition but does not allow the reagent to come in required proximity to the ketone. The reagent might thus have approached from the acetate side via coordination to deliver the hydride from below (Scheme 2-15).



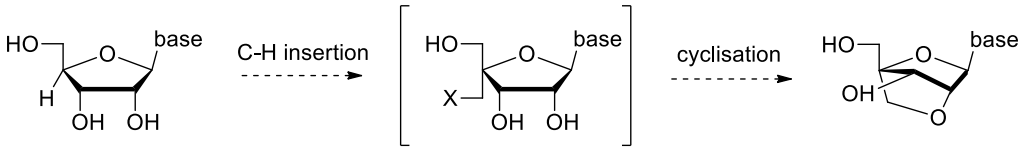
Scheme 2-15 Speculated rational for the unexpected *anti* reduction under several conditions.

Accordingly, the plan was to reduce the ketone in the open chain system. This approach, however, turned out to be very troublesome. Complex mixtures of diastereomers and TBS migration products

were obtained which were not separable and due to their similarity, peaks in the spectra strongly overlapped. Hence, the characterization was very difficult and often confusing. Pure compounds were not accessible or only in very small amounts. Giving the limited time we decided to put this approach on an indefinite hiatus.

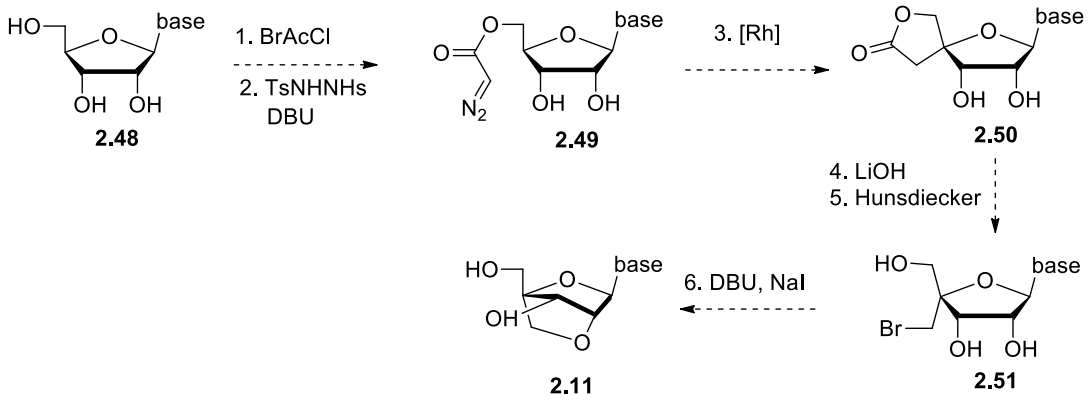
2.3.3 3rd generation: C-H insertion

After the disillusioning experience with a stubborn diastereoselective reduction we decided to completely revise our approach towards the LNA monomer. In fact, the only change in LNA compared to a commercial RNA nucleotide is the formal addition of a CH_2X unit at the 4'-carbon (Scheme 2-16) and the most elegant way to introduce this functionality would be via selective C-H insertion. The advantages of such an addition are clear: commercially available nucleotides, predefined stereo chemistry, short and direct reaction sequence.



Scheme 2-16 A C-H insertion at the 4'-carbon depicts the most elegant way towards the LNA monomer.

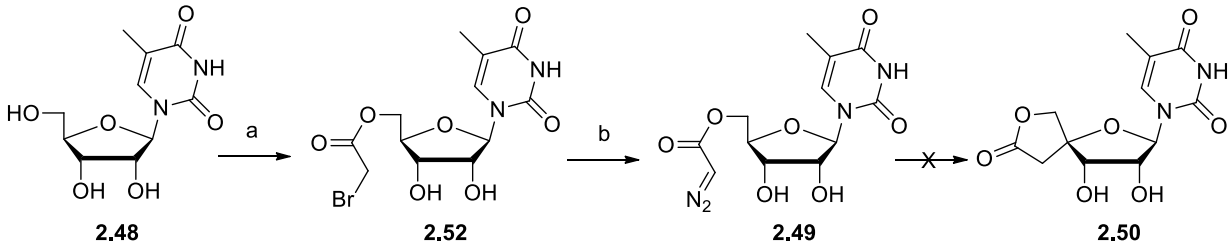
All the advantages of a C-H insertion come along with a major hurdle: selectivity. To our knowledge, there was no selective 4' C-H insertion reported yet. We therefore had to develop our own model but we quickly realized that probably the only way was an intramolecular C-H insertion. The 5'-position seamed a suitable position to introduce a diazo acetate (**2.49**), which in course could be used to form a metal carbene and insert into the 4' C-H bond to yield lactone **2.50** (Scheme 2-17). A subsequent lactone opening and Hunsdiecker reaction would give access to the desired methylene bromide **2.51** and allow a base induced ringclosure. In case bromides displaced equally bad as chlorides, NaI could be employed again.



Scheme 2-17 C-H insertion approach towards LNA monomers.

Fukuyama has developed a reliable method to introduce diazo acetates from alcohols[75] and it was an obvious choice to employ his methodology in our case. Furthermore, Rh-catalyzed 5-membered ring formations from diazo acetates are well described in the literature[76] and also an example of an acetalic C-H insertion[77] is reported (although only in a 6-membered ring formation).

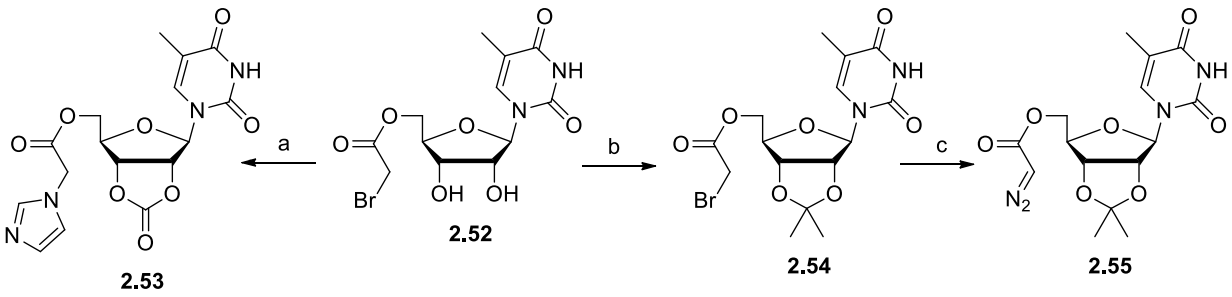
With good precedence we started the sequence with methyl uridine (**2.48**) and successfully introduced the bromo acetate giving **2.52** and transformed it into the corresponding diazo acetate **2.49** in moderate yield. The acetylation ran selectively and only 5' modification was observed, however due to solubility issues reproducible yields only between 15% and 35% were obtained (Scheme 2-18).



Scheme 2-18 Bromo acetylation and diazo foramtion: a) $NaHCO_3$, $BrCH_2C(O)Br$, MeCN, 0°C -> rt, 37%; b) $TsNH_2NH_2Ts$, DBU, THF, rt, 29%.

First attempts towards the lactone were not successful, mostly because diazo acetate **2.49** turned out to be sparingly soluble in common organic solvents. In addition, **2.49** was found to be highly hygroscopic, leading to sticky material, which was hard to deal with and making water free conditions almost impossible. We thus intended to protect the diol as a carbamate but because diazo acetates are not known for their high stability the protection was performed with the bromo acetate **2.52** (Scheme 2-19). While disuccinimidyl carbonate did not react with the diol, carbonyl diimidazol

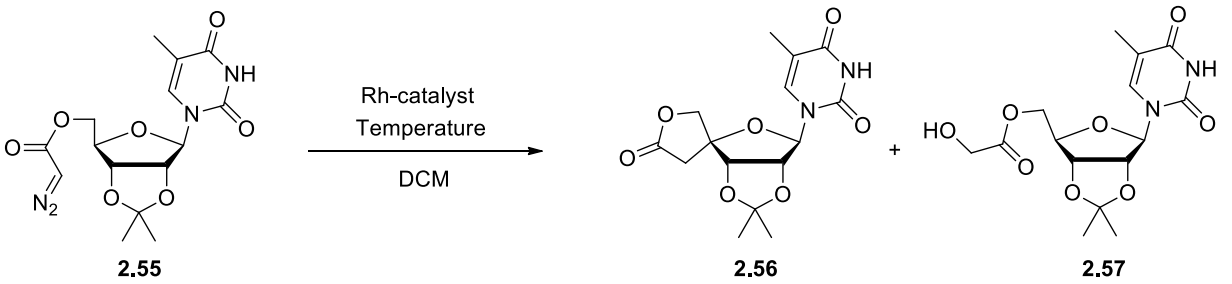
gave the desired product but the imidazole byproduct displaced the bromide, giving imidazole acetate **2.53** exclusively. We thus changed tack and intended to protect the diol as the corresponding dimethyl ketal. Without event, the desired protected diol **2.54** was synthesized in acceptable yield and was subsequently transformed into the corresponding diazo acetate **2.55** in high yield. We were pleased to find that diazo acetate **2.55** did not just form very nicely but was also proved to be a stable molecule, accessible in large amounts, poised for analysis of the key step.



Scheme 2-19 Protection of the diol as carbonate or ketal: a) CDI, MeCN, rt, 28%; $CH_3C(OMe)_2CH_3$, PPTS, DMF, rt, 69%; c) $TsNH_2NH_2Ts$, DBU, THF, 0°C -> rt, 82%.

The performed catalyst screening towards the C-H insertion was analyzed by UPLC-MS and is shown in Table 2-4.

Table 2-4 Attempted C-H insertion: Although water was rigorously excluded, the major product was the water insertion side product.



Entry	Catalyst	Temperature	Major product
1	$Rh_2(OAc)_4$	rt	**2.57**
2	$Rh_2(OAc)_4$	0°C -> rt	**2.57**
3	$Rh_2(OAc)_4$	-78°C -> rt	**2.57**
4	$Rh_2(OAc)_4$	0°C -> 40°C	**2.57**
5	$Rh(cap)_4(MeCN)_2$	rt	**2.57**
6	**3.3**	rt	**2.57**

Unfortunately the major product was in every case the water insertion side product **2.57**. Even under rigorously dry conditions the major product was the corresponding alcohol **2.57**, which shows how favored an O-H insertion versus a C-H insertion is. Entry 4 represented the most promising entry since a product in a vanishingly small amount was isolated which maybe could refer to the C-H insertion at the 3' carbon according to preliminary ^{1}H NMR- and mass spectroscopy.

2.4 Conclusion and future research

The invention of LNA and its analogues brought big innovations in drug discovery and the work in this chapter will hopefully contribute to this emerging field. Although the synthesis sequence was not finished, the synthetic work allowed for many insights into ribose carbohydrate chemistry. A *de novo* synthesis of the ribose frame was developed and free hydroxyl groups at the 1' and 2' carbon were found to lead to instability of the molecule but their acetylated moieties were stable. Further, it was discovered that TBS protecting groups are stable under silyl Hilbert-Johnson reaction conditions but also lead to unexpected results in *alpha* reductions. Another conclusive piece of work was the second ring closure: Chlorides proved to be suitable but not ideal. The addition of NaI was essential and should be employed in future from the beginning.

Concerning the reduction of the cyclic ketone ***rac* 2.35**, ruthenium catalyzed hydrogenation or a reduction with silicon hydrides should be performed as last options to probe whether the desired *syn* reduction can be achieved. If these measures also fail, a removal of the TBS group is suggested. A Cram chelate formation and reduction is expected to give the desired *syn* reduction product. Since the work described in chapter 2.3.2 only foundered on the reduction, a continuation and an excessive screening for reduction conditions would likely lead to success and an entry to affordable LNA monomers. Nevertheless, the obtained *anti* reduction product **2.44b** has the right stereochemistry for the synthesis of *xylo*-LNA (Figure 2-4). It was reported to have strong binding affinity to complementary DNA and RNA strands but only if the LNA strand was completely made of *xylo* backbones.[51]

Chapter 2.3.3 described the 3rd generation synthesis, which we feel is the most natural and elegant approach to LNA monomers. However, it is not necessarily meant to render the 2nd generation approach unimportant but to be complementary. This approach presents a challenge to a frontier area of synthetic chemistry: C-H insertion. Unfortunately, this synthetic plan was approached under severe time pressure and was run parallel to the 2nd generation synthesis which was inefficient for

both. However, a reliable synthesis of stable diazo **2.55** was developed, setting the stage for future work.

The catalyst screening was not comprehensive; many obvious possibilities could not be probed due to time restrictions. Du Bois' esp ligand needs to be investigated in the lactone formation and also more of the ligands and catalyst presented in chapter 3.2.1 merit testing. Further, conditions to avoid water in the reaction mixture need to be developed since water insertion was always the main product in a typical reaction setup so far. It is suspected that the water is coming from diazo **2.55**, as its precursors showed strong hydroscopic properties.

3 Modifiable ligands for lantern type Rh(II) complexes and their application in catalysis and in chemical biology

3.1 Introduction

3.1.1 Lantern type Rh(II) catalysts, the supremacy of tethered carboxylates and their application in catalysis

Lantern type rhodium complexes are dinuclear Rh(II)-Rh(II) scaffolds with four bidentate carboxylate ligands (Figure 3-1). Each ligand coordinates to both rhodium centers and occupies a quadrant, pointing along the (equatorial) y- and the z-axis. The d-orbitals along the (axial) x-axis remain free and are available for substrate interaction, making catalysis possible. This arrangement is sometimes also referred to as the paddlewheel structure.

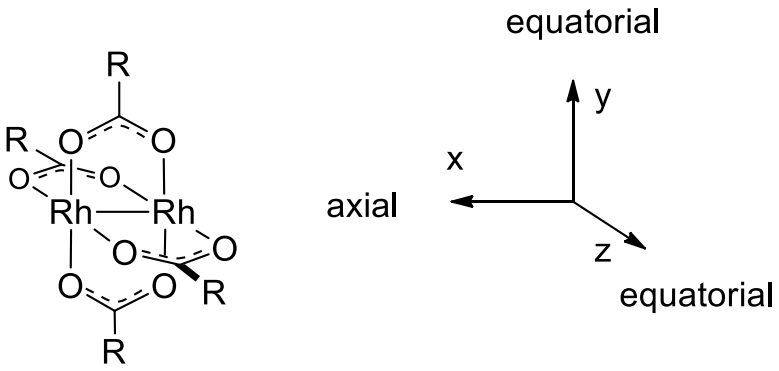


Figure 3-1 General structure of the lantern type dinuclear rhodium(II) complexes.

The most commonly employed reaction with Rh(II) acetates is the formation of Rh(II) carbenoids via decomposition of diazo precursors. The obtained carbenoids are a versatile class of reactive intermediates which undergo many types of X-H bond insertions: C-H[78], Si-H[79], N-H[80], O-H[81] or S-H[82] insertions were reported, intra- and intermolecularly. High functional group tolerance has been shown, making even late stage modifications via carbene formation in complex natural product syntheses viable[83]. Another widely used reaction is the cyclopropanation, which gives access to three-membered rings via rhodium carbenoids.

The basic structure of these complexes was developed into several subclasses of dinuclear rhodium complexes. For instance, chirality was introduced by employing chiral acetates or exchanging the acetates with optically active carboxamidates, allowing for enantioselective catalysis (Figure 3-2). Remarkable syntheses were accomplished with chiral rhodium(II) catalysts but since chirality does not play a role in the upcoming chapters, this highly interesting topic will not be further discussed in this introduction. For more information, the reader is referred to a review by Davies.[84]

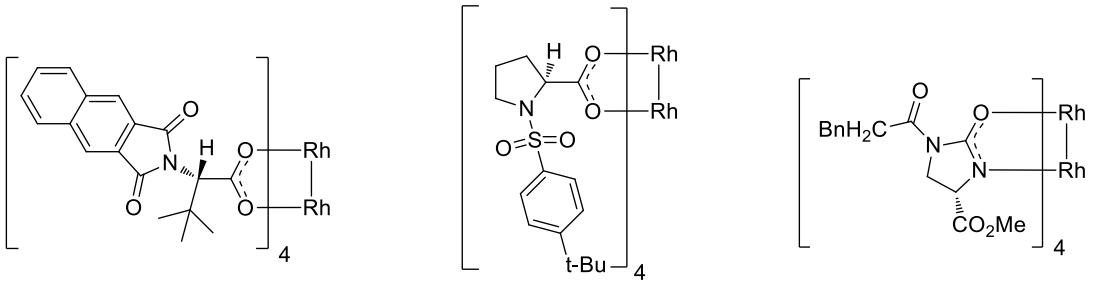


Figure 3-2 A selection of chiral ligands employed in enantioselective syntheses.

Another key subclass was made famous by Du Bois[85]. Inspired by the seminal work of Taber[86], Du Bois proposed that catalyst decomposition was partially due to ligand dissociation which could be reduced by tethering two carboxylates (Figure 3-3). In case of a carboxylate shift, the re-coordination to the metal center is entropicaly favored with a tether and thus higher turnover numbers were achieved.

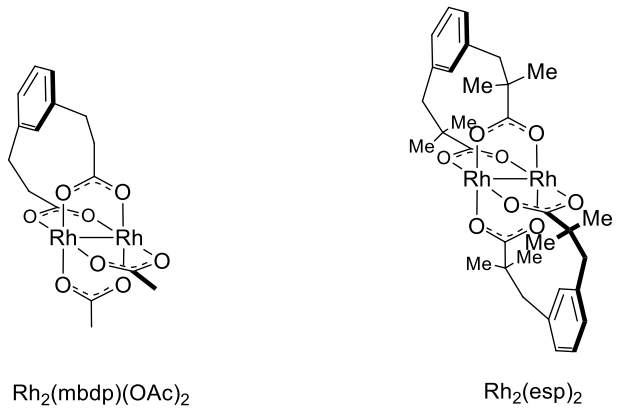
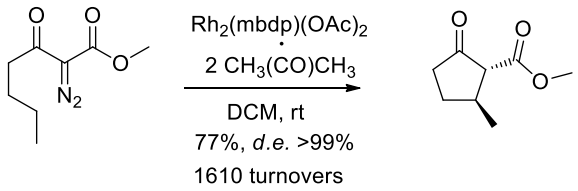


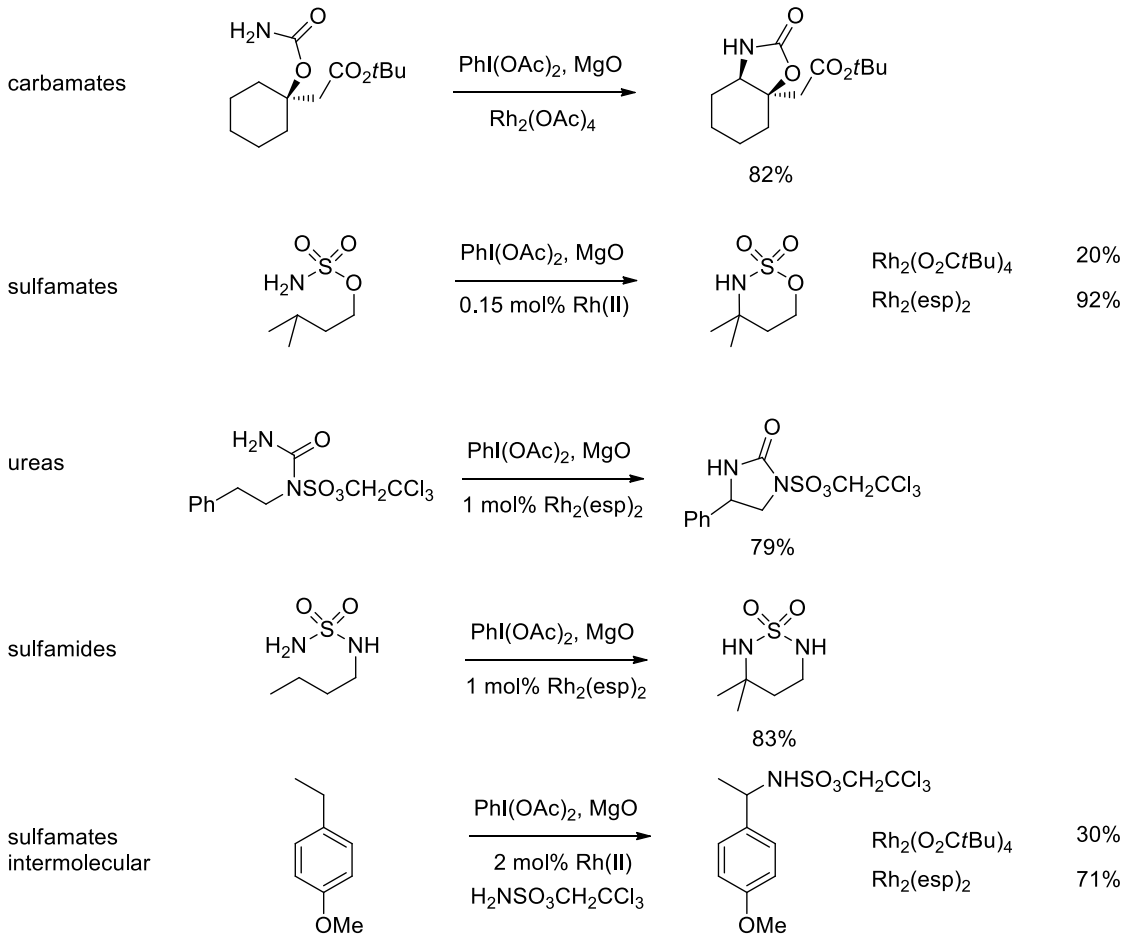
Figure 3-3 Du Bois' $Rh_2(esp)_2$, inspired by Taber's *m*-Benzenedipropionic acid ligand (mbdp).

Taber showed in his pioneering work[86] not only the first bridged dicarboxylate ligand, coordinating in bidentate fashion to a dinuclear rhodium(II) scaffold but also gave an example of a very efficient rhodium carbenoid C-H insertion reaction. An impressive turnover number of 1610, very high *d.e.* and good yield was reported (Scheme 3-1).



Scheme 3-1 First example by Taber, employing his bridged complex in a rhodium carbenoid C-H insertion reaction.

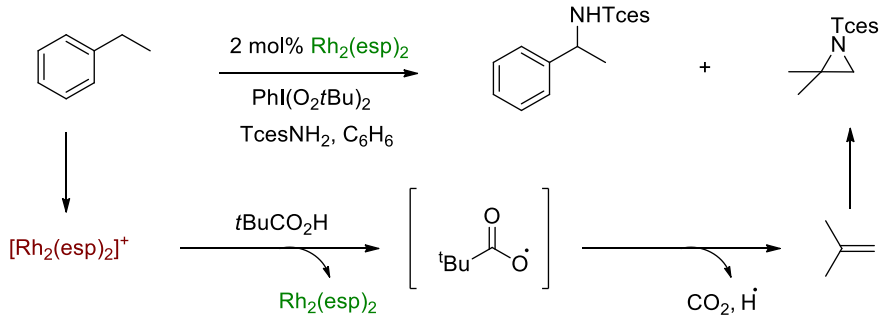
Du Bois extended the scope of rhodium chemistry from carbenes to nitrenes in his landmark publication in 2001.[87] Carbamates were oxidized by $PhI(OAc)_2$ to iminoiodinanes and then transmetalated on rhodium, giving rise to Rh(II)-nitrene complexes, subsequently inserting into C-H bonds.[88] The addition of MgO was found to be necessary in order to intercept formed AcOH, a byproduct of the oxidation with $PhI(OAc)_2$.



Scheme 3-2 Scope of current nitrene insertions with either non-tethered and tethered ligands.

Soon after, in 2004, the bidentate *esp*-ligand was introduced by Du Bois and it was shown that a tremendous increase in catalytic activity could be achieved, as well as a higher substrate scope.[85] Sulfamates, ureas and sulfamides were successfully transformed into their corresponding Rh(II)-nitrenoids and were used in intramolecular C-H insertions (Scheme 3-2). In the case of sulfamates even two examples of intermolecular nitrene C-H insertions were demonstrated. All reactions were run with maximum 2 mol% $Rh_2(esp)_2$ and clearly showed the supremacy over the non-bridged acetate ligands.

One of the reasons for the increased activity can certainly be attributed to the higher stability of complexes with chelating carboxylates compared to single acetate ligands (*vide supra*). Another reason was suggested after observing a color change from green to deep red during nitrene insertion reactions[89]. This observation was reported to be due to a one-electron oxidation to a mixed-valence Rh(II)/Rh(III) dimer, which can form if the C-H insertion is too slow to react with the nitrene on time. The difference between the much better performing $Rh_2(esp)_2$ and a conventional $Rh_2(OAc)_4$ catalyst turned out to be the ability of coping with the loss of an electron for longer time. The reduction to the active catalyst was also investigated and merits mention. The carboxylic acid, which forms during the oxidation (*vide supra*) was shown to reduce the Rh(III) under the formation of an *O*-radical species which subsequently decomposes to CO_2 and a hydrogen radical (Scheme 3-3). It was further found that due to electronic properties, *t*$BuCO_2H$ or even more $PhMe_2CO_2H$, are stronger reducing agents and facilitate the restoration of stable Rh(II)/Rh(II) species. As a consequence, it was demonstrated on a stubborn substrate that $PhI(O_2CMe_2Ph)_2$ was as the oxidant of choice.



Scheme 3-3 Du Bois' experiment to prove the reduction of Rh^{3+} by one elctron oxidation of a carboxylic acid.

3.1.2 Applications of Rh complexes in chemical biology

Dunbar studied the interaction and ligand exchang of dirhodium(II) complexes with nucleobases.[90] For instance, 9-ethylguanine is able to substitute an acetate and form stable complexes with Rh(II) (Figure 3-4). In further experiments, also short single stranded DNA fragments were successfully used in displacing the acetates to form a stable complex. It is noteworthy that the interaction of N7 and O6 in guanine or N7 and N6 in adenine with Rh(II) leads in either case to significant change of the pK_a of N1. The same observation had already been seen with *cis*-platinum, a potent anti-cancer drug, and suggests that the metal coordination severely impairs with usual Watson and Crick base pairing. The result is metal mutagenicity and cell death[91]. Accordingly, dirhodium(II) complexes bode well for anti-tumor therapeutic agents and are worthwhile to be studied.

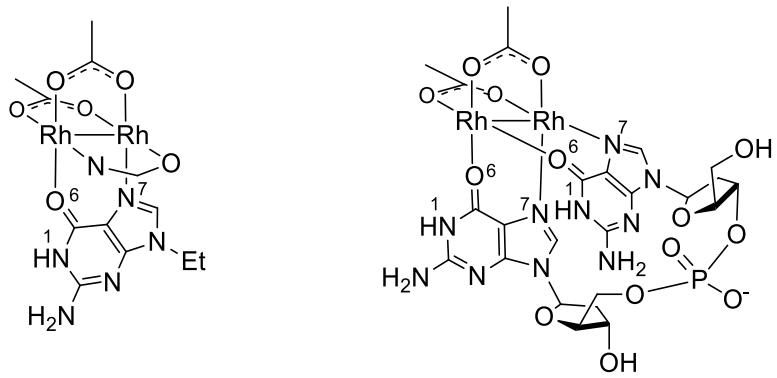
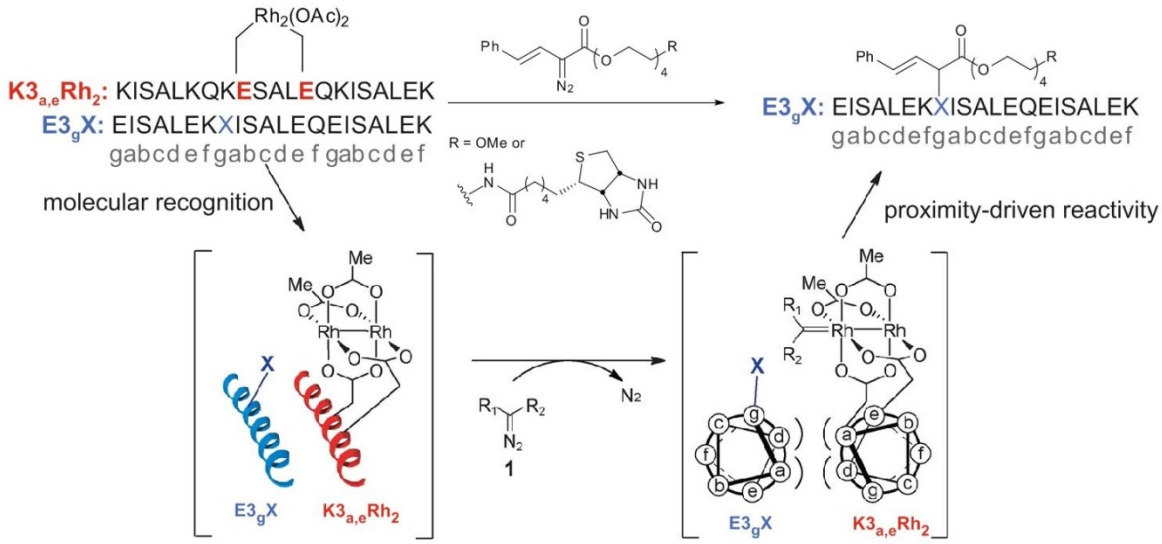


Figure 3-4 Interaction of Rhodium acetate: stable complexes with Et-Guanine or Guanine in short ssDNA.

Dunbar further studied the fate of Rh(II) complexes in cells.[92] A fluorescent bodipy label was attached to a phenantroline which was then complexed with $Rh_2(OAc)_4$. The resulting fluorescent probe was incubated with lung cancer cells and then traced by confocal fluorescence microscopy. An accumulation in lysozyme and mitochondria was found, but no Rh-dye reached the cell nucleus; an unfortunate reality, regarding Rh(II)'s anti-cancer potential. Nevertheless, it was shown that the distribution of the fluorophore-Rh(II) complex in the cells differed from free fluorophore and suggests that ligand and dye modifications could be exploited to determine the place of accumulation of Rh(II) in cells.

Another great example of Rh(II) in chemical biology was published by Ball (Scheme 3-4).



Scheme 3-4 Templated chemistry: Coiled coil interactions allowing for site selective coil modification possible.

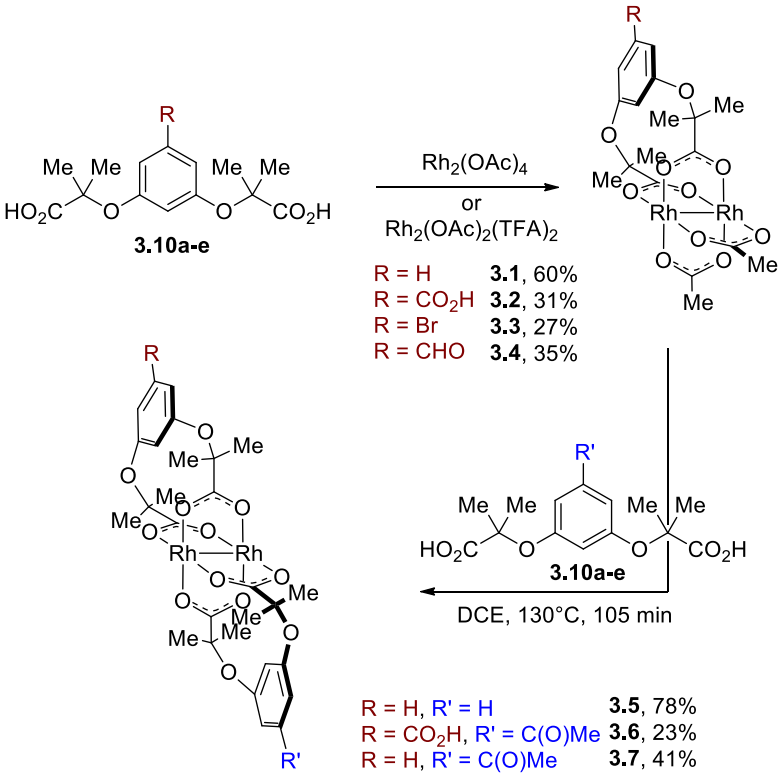
Rhodium was introduced into peptide coils, where carboxylates in the side chains act as chelating bidentate ligands.[93] This catalyst construct was then applied in site selective peptide modification exploiting a coiled-coil assembly. A water soluble diazo substrate was employed which underwent carbenoid formation with the rhodium und subsequently inserted into polar bonds. If the Rh(II) was coordinating to two glutamic acids at helix position a and e, modification was found exclusively at the g position in the opposite helix. A variety of amino acids were labeled by either O-H (Tyr, Ser, Asp, Glu), N-H (Trp, Arg, His, Gln, Asn), S-H (Cys) insertion or cyclopropanation (Phe). This method showed once again the power of Rh(II) in biological systems and should motivate to further development of Rh(II) lantern complexes in chemical biology.

3.2 Synthesis

3.2.1 Ligands, complexes and catalysis

The results found in this chapter (3.2.1) are the cumulative work of the author of this theses (D.B)(ligand-, complex synthesis, benchmark reactions), Pascal Schmidt (ligand-, complex synthesis, benchmark reactions), Stefanie Geigle (benchmark reactions), Antoinette Chougnet (ligand-, complex synthesis) and Wolf-Dietrich Woggon (ligand-, complex synthesis).

We became interested in tethered bis-dicarboxylate rhodium(II) complexes in the context of our recent studies on metal-carbenoid based nucleic acid alkylation.[94] To further develop this technology we needed a set of rhodium(II) complexes with stable and modular ligands that still performed well in synthetic processes. Most rhodium complexes are highly insoluble in water and not readily amenable to modification.[95-99] We settled on the tethered bis-carboxylate structure because we thought its increased stability,[100] as well as its potential to intercalate DNA,[90] could deliver performance improvements in comparison with $Rh_2(OAc)_4$. The ligand introduced by Du Bois and co-workers[85] was chosen as a starting scaffold but two major problems prompted us to change tack: first, creating a library of ligands proved synthetically cumbersome and second, controlling mono- versus double-substitution in the rhodium carboxylates was unpredictable. Inspired by previous work from Bonar-Law in creating dirhodium-based metal-organic architectures,[101-104] we examined dicarboxylate ligands derived from 1,3-benzenediols (Scheme 3-5).

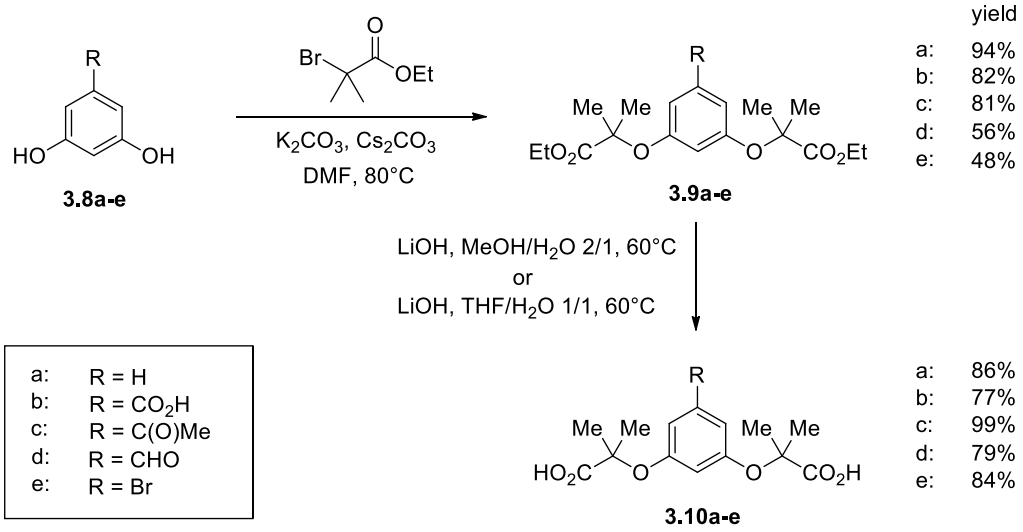


Scheme 3-5 Modular approach towards mono- and bis-substituted rhodium(II) complexes.

This construct maintains the essential structural features of the espino ligand, but has the advantage of modularity since numerous 1,3-benzenediol derivatives are commercially available. Moreover, since Bonar-Law used these dicarboxylates to create well-defined supramolecular objects the coordination of each ligand needed to be precisely controlled, providing valuable information for our own studies.

The syntheses of the various homo- and heteroleptic rhodium(II) complexes we have prepared are shown in Scheme 3-5. Using the conditions developed by Bonar-Law the monobiscarboxylate complex **3.1** is obtained in 60% yield after three hours in *N*,*N*-dimethylaniline. However, for ligands with electron withdrawing groups at C5 (**10b**-**d**) milder conditions were necessary: $Rh_2(OAc)_2(TFA)_2$ in DCE at 60-70°C with small amounts of EtOAc as co-solvent led to acceptable yields (31% for **3.2**, 27% for **3.3**, and 35% for **3.4**). Unfortunately, attempts to perform a second substitution to access the heteroleptic complexes using Bonar-Law's conditions led to low yields and mixtures of products. We therefore turned to Taber's original procedure involving a portion-wise addition of the ligand.[86] Through the combination of these protocols we have been able to synthesize new rhodium(II) complexes containing a variety of functional groups (Scheme 3-5). The yields are low to moderate, but this is a typical feature of syntheses of rhodium(II) complexes; in many cases substantial amounts of starting material can be recovered and recycled.

Shown in Scheme 3-6 is the full collection of dicarboxylate ligands **3**.**10a-e** we have synthesized thus far starting from commercial C5-substituted 1,3-benzenediols **3.8a-e**. Diesters **3.9a-e** were synthesized by double O-alkylation with ethyl-2-bromoisobutyrate and a mixture of K_2CO_3 and Cs_2CO_3 in yields between 77 and 99%. Final hydrolysis was accomplished with LiOH to afford the desired dicarboxylate ligands **10a-e** in excellent yield, bearing a variety of functional groups poised for further modification such as amide bond formation (**3.2** or **3**.**6**), Pd-catalyzed cross coupling (**3**.**3**) or condensation reactions (**3**.**4**, **3.6**, **3.7**).

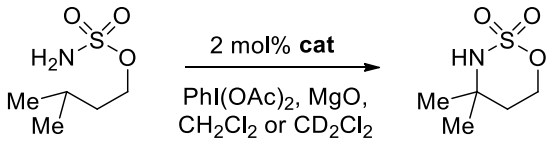


Scheme 3-6 Ligand synthesis by ether formation and subsequent ester hydrolysis. Compounds 8a-e are commercially available. Yields of 3.9a and 3.10a according to Bickley.[101]

To probe the impact of the ligand on catalysis dirhodium(II) catalysts **3**.**5**, **3.6**, and **3.7** were tested in a typical intramolecular nitrene insertion reaction of sulfamate ester **3.11** (Table 3-1). Catalyst **3.5** leads to reaction at a similar rate as the Du Bois catalyst (see entries 1 & 2); only at 0.1 mol% loading does the Du Bois system prove superior,[85] still delivering complete conversion while **3.5** stalls at 35% (data not shown). For operational simplicity and to allow comparisons at early time points reactions with catalysts **3.5-3.7** were also run at 25 ˚C. At 25 ˚C **3.5** reached complete conversion in 2 hours (entry 3), while **3.6** required 4 hours (entry 4). Catalyst **3.7** performed best of all, giving complete conversions at 60 minutes (entry 5). Catalyst **3.7** was further tested with some potential interfering additives to determine its robustness.[105] We chose protic or Lewis basic additives since our primary goals are for aqueous catalysis. Although methanol and acetic acid both attenuate the reactivity of **3.7**, complete conversions were still achieved in reasonable reaction times (entries 6 & 7). The powerful Lewis base trimethylamine, however, inhibited the reaction (entry 8). The superiority of catalyst **3.7** in nitrene insertion may be a result of the more electron deficient character of the ligand,

which would make the catalyst difficult to oxidize as mentioned earlier. Du Bois has shown that oxidative damage to catalysts is the primary mode of catalyst deactivation in nitrene insertion (*vide supra,* Scheme 3-3).[89]

Table 3-1 Benchmarking of catalysts in a nitrene insertion.



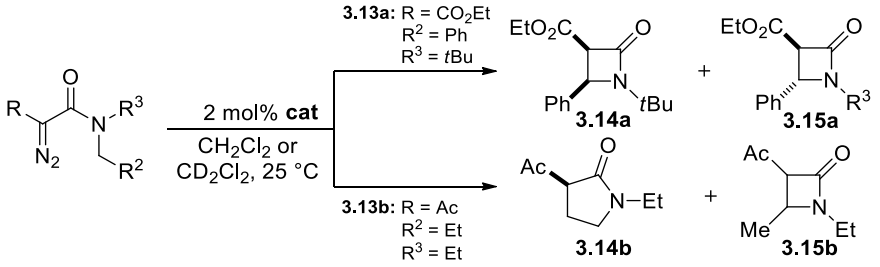
3.11 **3.12**

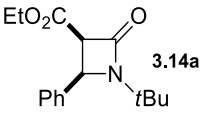
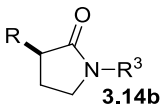
Entry	Catalyst	Additive	Temp [°C]	Time [min][a)]
1	**3.5**	-	40	45[b)]
2	$Rh_2(esp)_2$	-	40	45
3	**3.5**	-	25	120[c)]
4	**3.6**	-	25	240[c)]
5	**3.7**	-	25	60[c)]
6	**3.7**	MeOH	25	120[c)]
7	**3.7**	AcOH	25	240[c)]
8	**3.7**	NEt_3	25	n.r.[c)]

[a)] time to reach ≥95% conversion; [b)] 98% isolated yield after chromatography; [c)] determined by ^{1}H NMR monitoring of the reactions in CD_2Cl_2

In a second set of benchmarking experiments the new set of catalysts were tested in C-H insertion reactions to make β- or γ-lactams (see **3.14a** and **3.14b** in Table 3-2).[106] Comparison of entries 1-4 indicate that **3.5** performed best for β-lactam formation by C-H insertion. This trend was also seen in the formation of a γ-lactam (cf. entries 8-11), although with this substrate **3.7** also worked well. The reaction times of 20 and 10 minutes for the reactions in entries 2 and 9 respectively represent a new standard for this class of transformations. As a point of comparison the conditions in entry 8 are the previous best results for this transformation; here higher loading (3 mol%), higher temperature (70 ˚C in toluene), and a longer reaction time were needed (60 minutes).

Table 3-2 Benchmarking of catalysts on C-H insertion reactions.



Entry	Catalyst	Additive	Product	14:15[a]	Time [min][b]
1	$Rh_2(OAc)_4$	-	 3.14a	19:1	270[b]
2	**3.5**	-	**3.14a**	>49:1	20[c]
3	**3.6**	-	**3.14a**	>49:1	120[b]
4	**3.7**	-	**3.14a**	>49:1	60[b]
5	**3.5**	MeOH	**3.14a**	>49:1	30[b]
6	**3.5**	AcOH	**3.14a**	>49:1	150[b]
7	**3.5**	NEt_3	**3.14a**	-	n.r.
8	$Rh_2(OAc)_4$	-	 3.14b	4:1	60[b]
9	**3.5**	-	**3.14b**	9:1	10[d]
10	**3.6**	-	**3.14b**	8:1	60[b]
11	**3.7**	-	**3.14b**	9:1	10[b]

[a] Ratio measured by ^{1}H NMR analysis of crude reaction mixtures[b] time to reach ≥95% conversion determined by ^{1}H NMR monitoring of the reactions in CD_2Cl_2; [c] 76% isolated yield after chromatography; [d] 80% isolated yield after chromatography

The modularity of the catalyst system opens new vistas in controlling rhodium-carbene chemistry. For example, although aqueous rhodium(II) catalysis is well-established, moderate water solubility limits the scope of most catalysts. Catalysis in water has therefore been limited to soluble variants,[107,108] systems that contain cosolvents or detergents,[109] or for catalysts bearing peptide ligands.[110] The emerging importance of rhodium catalysis in chemical biology demands that more efficient water-soluble systems be developed.[111-113] The heteroleptic dirhodium(II) complex **3.6** bearing a ketone functionalized ligand (**3.10c**) and a carboxylate functionalized ligand (**3.10b**) was found to be completely water soluble above the pK_a of the carboxylate. This simple feature of complex **3.6** is representative of the power of modularity in controlling the bulk properties of a catalyst. As a proof-of-concept for the potential of **3.6** in aqueous catalysis we carried out two different types of reactions under aqueous conditions: The first was a simple O-H insertion with water (Figure 3-5), and the second a C-H insertion of compound **3.13a** (Scheme 3-7). In both cases

catalyst **3.6** outperforms the previous best case. For the O-H insertion **3.6** was compared to $Rh_2(OAc)_4$ and although both catalysts only led to approximately 80% conversion, **3.6** achieved this plateau in 70 minutes while $Rh_2(OAc)_2$ required 150 minutes.

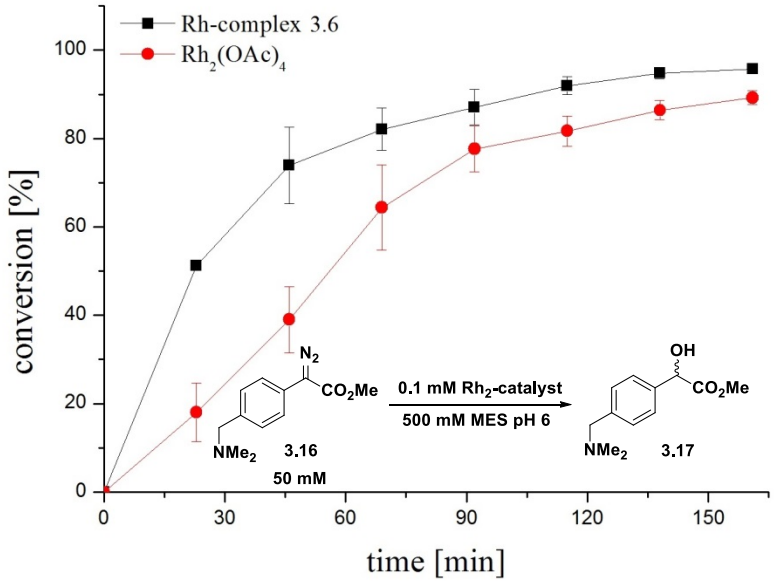
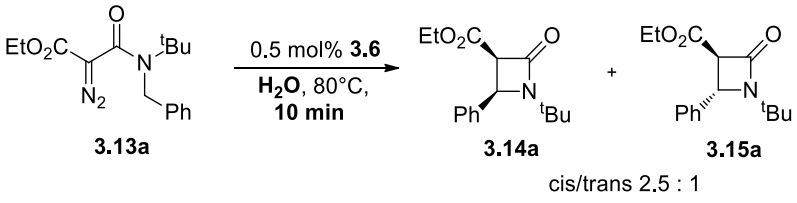


Figure 3-5 Complex 3.6 reaches the first half-life approximately twofold faster than $Rh_2(OAc)_4$; the early inflection point for the red curve suggests a catalyst activation step.

In the intramolecular C-H insertion, catalyst **3.6** required lower loading (0.5% vs 1-2%) and less time (10 min vs 0.5-24h) than the previous best catalyst.[107,108] Dirhodium(II) catalysts with high TOF in water are rare and therefore catalyst **3.6** represents a good candidate for future development in aqueous catalysis.



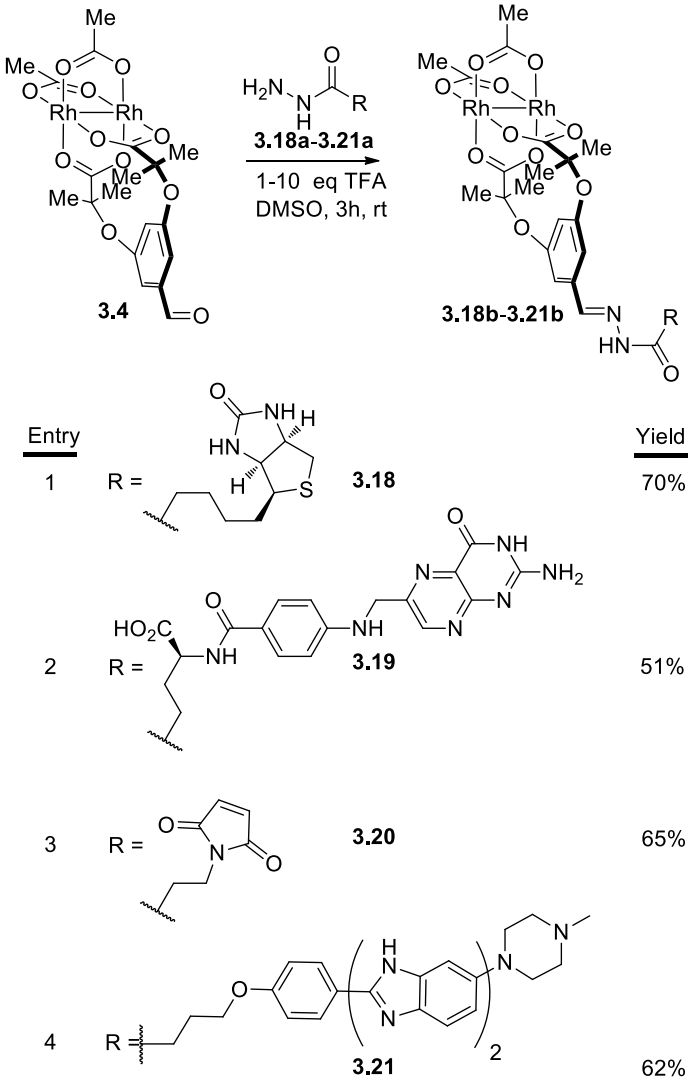
Scheme 3-7 Benchmark reaction for aqueous carbene insertion shows full conversion in 10 minutes.

3.2.2 Late stage modification with hydrazides and application in chemical biology

We designed the ligand to combine structural flexibility without perturbing rhodium's primary ligand sphere, thus facilitating sophisticated modifications of the rhodium complexes (Table 3-3). Aldehyde-bearing complex **3.4** was condensed with a variety of hydrazide derivatives of small molecules that are important in chemical biology to create dirhodium(II) complexes with tailored properties. In particular conjugates with biotin, folic acid, maleimide, and Hoechst dye were all prepared without event. The maleimide and biotin complexes could be used in metalloenzyme development;[114,115] while biotin could also be used for directing the catalyst to histones,[116] potentially offering a way to modify them

.

Table 3-3 Conjugation of complex 3.4 with a variety of useful small molecules.



Many dirhodium(II) complexes have been shown to have DNA binding properties comparable with cisplatin;[90] and the folate receptor is known to be overexpressed in cancer cells due to increased nutrient requirements.[117,118] By combining these properties, folate-rhodium conjugates might therefore provide cancer-selective cytotoxins. The γ–acid of folate has previously been shown to be amenable to modification without interfering with receptor binding[119] and we were pleased to find that a hydrazide installed at this position led to smooth and selective condensation with complex **3.4** (Table 3-3, entry 2).

Condensation products **3.18b**-**3.21b** were obtained as a mixture of two similar products, which were determined to be s-*cis* and s-*trans* isomers due to restricted rotation of the C-N bond in the hydrazone. They can easily be differentiated by their chemical shift in the ^{13}C NMR spectra.[120] The stereochemistry of the hydrazide double bonds was found to be exclusively *trans* according to the NOESY spectra of **3.19b** (Figure 3-6).

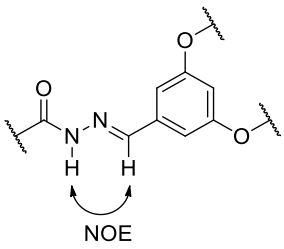


Figure 3-6 NOESY cross peak suggesting a *trans* double bond of the hydrazide.

It has also recently been shown that fluorescently labelled dirhodium(II) complexes are taken up by cells and accumulate in lysosomes and mitochondria.[92] No dirhodium(II) could be detected in the nucleus, an unfortunate reality given that dirhodium(II)'s antiproliferative activity is likely a consequence of its interaction with DNA.[121,122] We envisioned reprogramming the cellular fate of rhodium by attaching a traceable molecule known to target DNA and we selected the common nuclear staining dye Hoechst 33258 for proof-of-concept (Table 3-3, entry 4).

The preparation of the needed aqueous samples, however, turned out to be challenging. Even though the required concentrations of the Rh-dye were as low as 1 – 100 μM, no homogeneous solutions could be made in pure PBS buffer, which is the most commonly used buffer for cell essays (i.e LSM imaging). Also a pH 6.5 MES buffer was not suitable to protonate the alkaloid and to bring it into solution. After a small solubility study it was found that dye-adduct **3.21b** can be dissolved in many polar solvents: DMSO, MeCN, MeOH and also ethylene glycol. While MeCN and MeOH are considered to be rather cytotoxic, living cells can handle a certain amount of DMSO or ethylene glycol. Thus, 100 μM solutions of **3.21b** in DMSO and ethylene glycol were made, but the 10-fold

dilution with PBS buffer resulted in precipitation. As a further measure, a 100 μM solution of **3.21b** containing 0.01% Triton-X detergent was made and indeed this stock solution could be diluted by a 10-fold with PBS without observable precipitation.

The excitement after Triton-X was found to help dissolve Rh-dye **3.21b** was big, but incubation experiments and LSM imaging with this sample quickly revealed, that the solution was not found yet and no cell nuclei were stained. The key finding was done in the third series of cell staining: According to the standard assay protocol, the stain was usually diluted once more with PBS for incubation. This process turned out to cause problems for the stain since it probably led to precipitation in the wells (Table 3-4, entry 1-4).

Table 3-4 Third series of staining, revealing that incubation with too much PBS precipitatated the Rh-dye 3.21b

Entry	Conc. of **3.21b**	Solvent	Diluted with PBS	Nuclear staining
1	100 μM	EtGly	Yes	No
2	100 μM	EtGly, 0.005% TrX	Yes	No
3	1 mM	EtGly, 0.05% TrX	Yes	No
4	100 μM	10% EtGly in PBS, 0.005% TrX	Yes	No
5	100 μM	10% EtGly in PBS, 0.005% TrX	No	**Yes**
6	100 μM	50% EtGly in PBS	No	**Yes**

Entry 5 and 6 in Table 3-4 show that if no dilution on the plate was performed, a nuclear staining was observed. The conditions of entry 5 gave staining as efficient as in entry 6, however the cells seemed to be under more stress. This observation is likely due to the Triton-X. The final results with the conditions of entry 6 are shown in Figure 3-7.

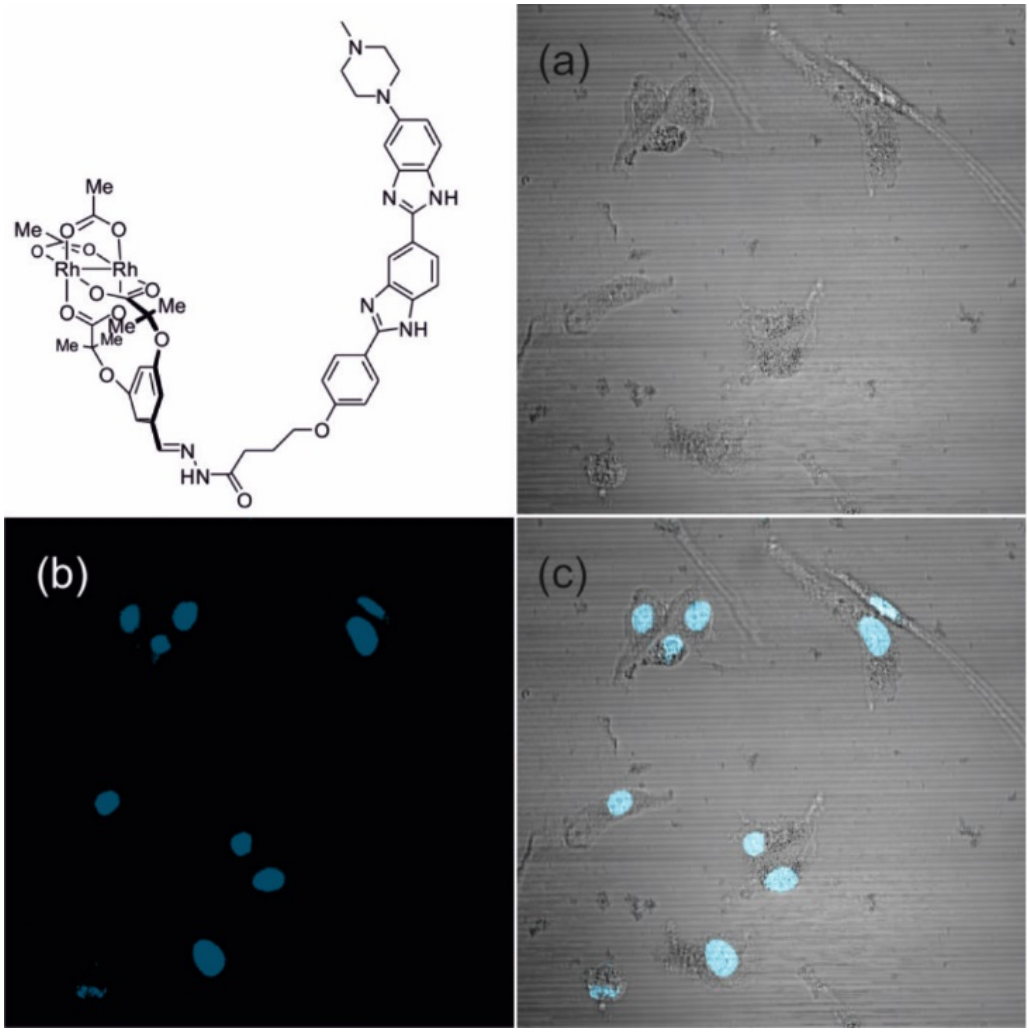
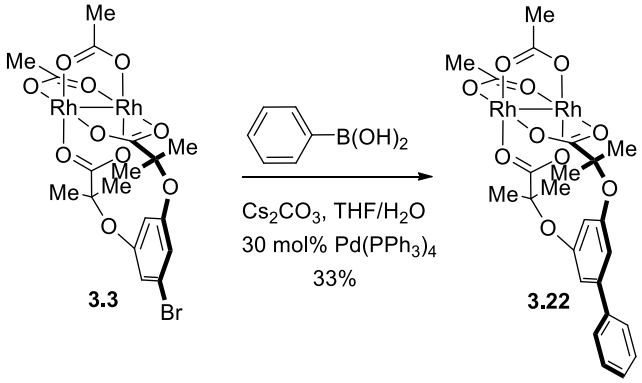


Figure 3-7 Selective Rh(II) complex uptake into cell nuclei of live U87 cells: (a) cells under white light, (b) cell nuclei stained by complex 3.21b, (c) overlay.

3.2.3 Catalysis on a catalyst

Modularity is a crucial component of catalyst optimization, we therefore explored the unconventional possibility of modification of our rhodium(II) catalysts via palladium catalysis. We synthesized ligand **3.10e**, containing an aryl bromide and made the bromo complex **3.3** (Scheme 3-5). Under un-optimized conditions it was in fact possible to arylate complex **3.3** in moderate yield by Suzuki cross-coupling to obtain the biaryl complex **3.22** (Scheme 3-8).

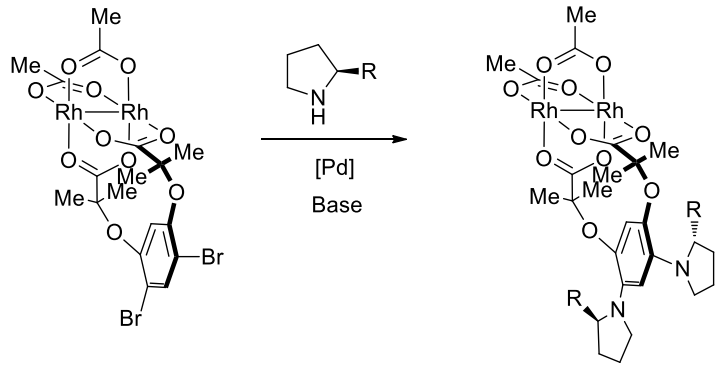


Scheme 3-8 Suzuki cross coupling on rhodium complex 3.3

Although the reaction worked, some improvements would be required to achieve a practical process. For instance it appears that the employed $Pd(PPh_3)_4$ does act as an almost stoichiometric reagent, rather than a catalyst. Ligand dissociation off the palladium(0) is needed to initiate the catalytic cycle. A displacement of the acetates on the rhodium(II) is unlikely, especially with bridged ligands but there are still the axial positions to coordinate to. Phosphine scavenging due to coordination to rhodium could likely lead to early Pd-catalyst decomposition. Nevertheless, this is to our knowledge, the first example of a metal catalyzed reaction happening on a ligand of a metal complex.

3.3 Conclusion and perspective

In this work we combined the powerful tethered carboxylate ligands, added the innovation of handles to easily allow for late stage modification, and showed their high performance in catalysis. One of the key decisions turned out to be the use of Bonar-Law's scaffold instead of Du Bois' known catalytically active "esp" ligand set-up. Since 5-susbtituted resorcinols are readily available in great varieties, Bonar-Law's ligand frame allowed us to easily introduce functionality at the 5-position but no precedence for their catalytic activity was given. We were therefore delighted to discover that our modified catalysts performed comparable or even better than the state-of-the-art catalysts in a number of reactions. In-depth studies of these complexes would make a worthwhile contribution to the organometallic, catalysis, and chemical biology community. As a starting point, the influence of the ether bond compared to the benzylic CH_2 in the "esp" ligand would give an insight about the characteristics of the resorcinol based ligands. Dissociation constants, pK_a of the di acid and also the half-lives of the oxidized rhodium complexes would give a deeper understanding and of their activity and could guide further developments of better catalysts. Concerning further catalytic reactions, the catalysts should be tested in cyclopropanation and aziridine formations. An even more exiting breakthrough would be a general protocol for intermolecular nitrene C-H insertions since Du Bois only published two examples of those and where the Tces protecting group was strictly required and not so useful molecules were made. On the other hand, the herein presented complexes allow for late stage introduction of chirality by cross coupling. For instance, by Buchwald-Hartwig coupling with proline derivatives on the known dibromide[101] (Scheme 3-9). Whether the chiral induction at position 4 and 6 of the aromatic backbone will have an impact on the stereo chemical outcome of a chemical reaction needs to be investigated.



Scheme 3-9 Proposal of chiral bidentate ligands based on the successfully applied scaffold.

In the field of chemical biology and drug discovery, folic acid conjugate **3.19b** should be studied as a cancer therapeutic agent. The combined properties of Rh(II) binding to DNA, hydrazides as common

and stable linkers under physiological conditions and folic acid as a well-known molecule director into tumor cells, make adduct **3.19b** an obvious choice to fight cancerous cells in a controlled way. A collaboration with an experienced research group in oncology would be of use and allow a maximal exploitation of the chemistry developed in our labs.

Hoechst-adduct **3.21b** was successfully introduced into U87 cancer cells and sets the stage for further investigations towards DNA or histone modification in the nucleus. The synthesis of a Hoechst-Diazo substrate should be possible and could be then incubated with **3.21b** and cancer cells. Cell lysis and subsequent gel electrophoreses would reveal if DNA was modified in the cell nucleus. However, before this task can be tackled, water solubility of the adduct needs to be increased. Although the results in Figure 3-7 were very promising, a closer look also revealed that the cells suffered under the high ethylene glycol content. To solve this problem a PEG chain could be introduced between the ligand and the dye. Hence, the challenge will likely be to find the right balance between lipophilicity to penetrate the cell membrane and the hydrophilicity to make the molecule water soluble.

4 Attempted hydroxylamine synthesis by direct alcohol amination giving access to *N*-(*t*-butoxy)carbamates

4.1 Introduction

4.1.1 About hydroxylamines

Hydroxylamines are molecules with a basic structure where a nitrogen atom is connected with a single bond to an oxygen. Unsubstituted hydroxylamine is an inorganic compound, which can be isolated as unstable and hygroscopic white crystals. More frequently, hydroxylamine is handled as an aqueous solution.

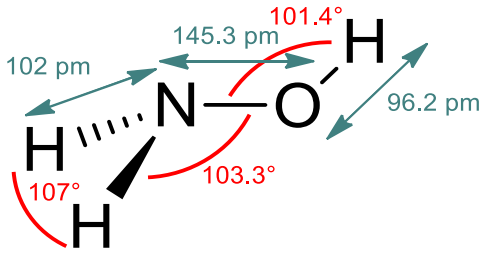


Figure 4-1 Measured bond length (in blue) and dihedral angles (red) of unsubstituted hydroxylamine.

The bond length in unsubstituted hydroxylamine was measured by microwave spectroscopy and determined to be 145 pm. This bond length is comparable with a sp^2-sp^2 carbon-carbon bond (Figure 4-1).[123] The shown *trans* structure is favored by 3.9 kcal/mol over the *cis* structure and substituted hydroxylamines can be N-, O-, or N,O-substituted and occur in different patterns in nature.

A very prominent example is the natural product Calicheamicin γ1 shown in Figure 4-2.

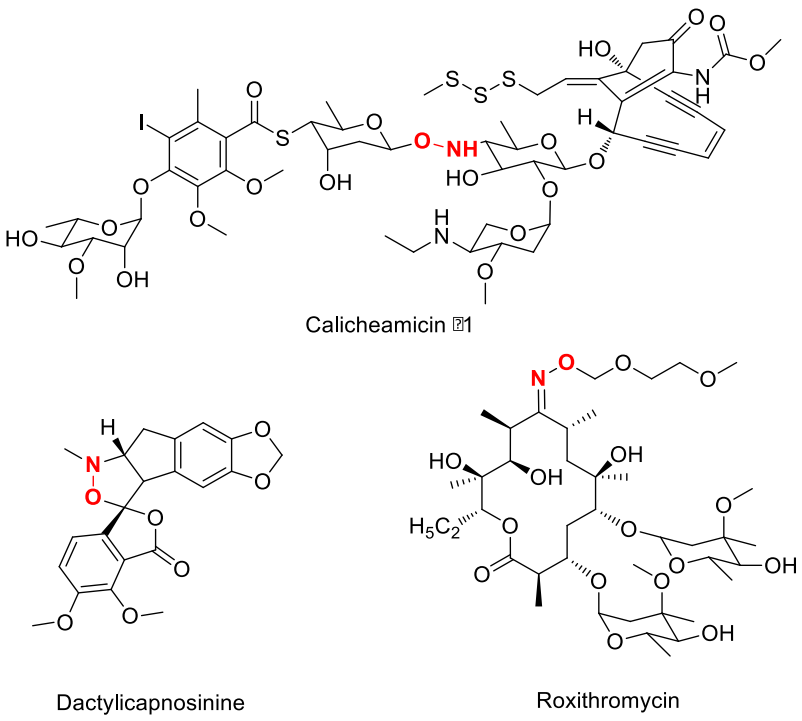
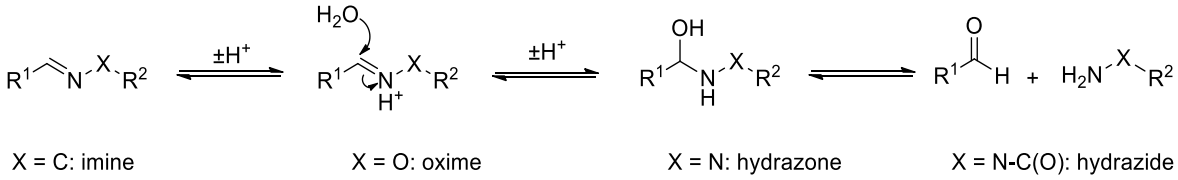


Figure 4-2 Natural and semi-natural products containing hydroxylamine building blocks.

This enediyne antitumor antibiotic was isolated from *Micromonaspora echinospora* in 1987 in Texas and features a hydroxylamine as the glycosidic bond between the two central sugars. Other natural products, such as Dactylicapnosinine, incorporate hydroxylamines as isooxazolidines. Dactylicapnosinine was isolated in 1995 from the Chinese medicinal plant *Dactylicapnos torulosa* by Steinbeck *et al.*[124] Another motif of hydroxylamines in complex molecules is in form of a O-alkyl oximes. Roxithromycin is a current antibiotic used against bacterial ear, nose, and throat infections. It derived from the natural product Erythromycin by condensation of an O-alkyl hydroxylamine terminated ether chain with the ketone of the macrolide.

The Schiff base in Roxithromycin from the hydroxylamine and the ketone seems to be a rather labile construct at first sight; however those oximes show a surprisingly high stability against hydrolysis.[125] Whereas the Schiff base of a conventional amine, the imine, has its equilibrium on the starting material side, hydroxylamines form oximes with a strong preference for the condensed product.

This observation is due to the *alpha effect*, induced by the increased electronegativity of the adjacent oxygen. It was shown that the process of hydrolysis is initiated by a protonation (Scheme 4-1) of the nitrogen followed by the attack of water, where the efficiency of protonation correlates directly with the electron withdrawing potential of the adjacent atom, since the ability of the N-lonepair to coordinate to a proton is reduced.[125]

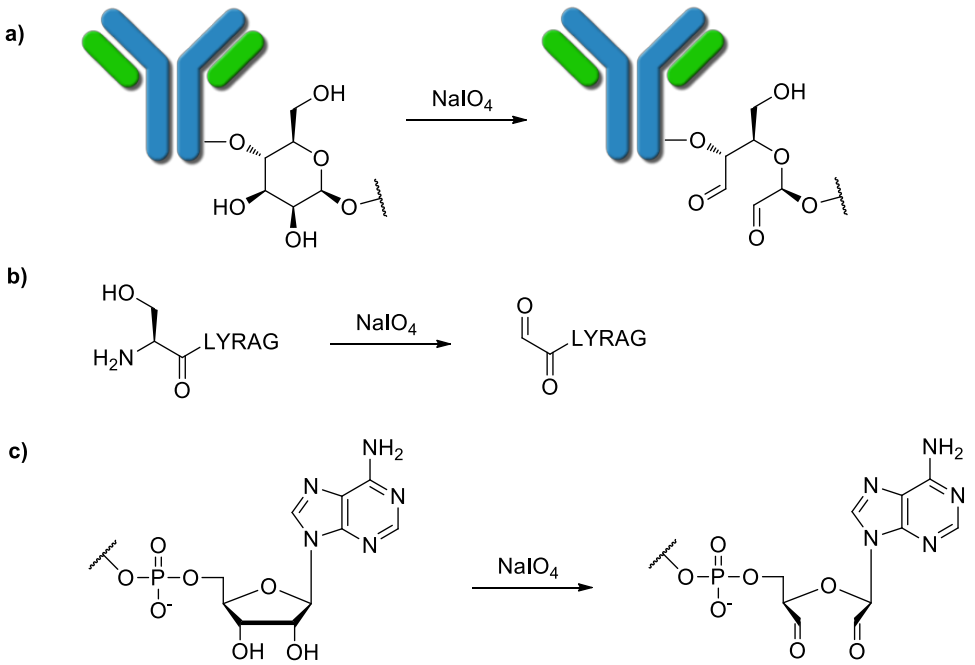


Scheme 4-1 Putative mechanisme for the hydrolysis of oximes, hydrazones and hydrazides.

This allows the following conclusion in terms of stability against hydrolysis: Imine << hydrazone < hydrazide < oxime.[125]

4.1.2 Application of hydroxylamines in chemistry and chemical biology

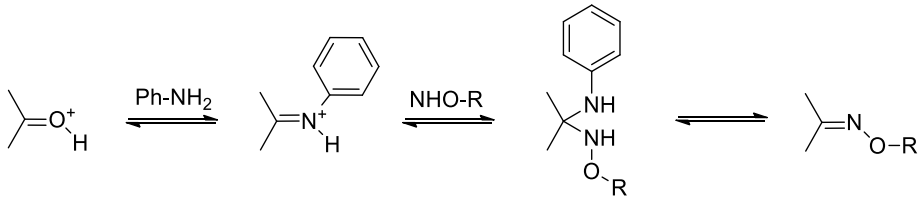
Although there are cases of hydroxylamines in natural products, the main application of hydroxylamines is in the field of bio-conjugation. In order to probe biological processes on a chemical level, scientists find themselves nowadays in the situation needing techniques to covalently bind tags (e.g. fluorophores or pharmaceutically active molecules) to biological macromolecules or connect two macromolecules together (e.g. Antibody and enzyme)[126]. For such applications, chemoselectivity, robustness, and short reaction times under physiological conditions are crucial. Since aldehydes and ketones are often readily available (see erythromycin) or can be introduced with ease into short peptides[127], proteins[128], terminal RNA-nucleotides,[129] antibodies[130] or even cell surfaces[131] by glycoside oxidation with $NaIO_4$, chemical ligation by condensation seems an obvious choice. Representative examples of oxidation by $NaIO_4$ are shown in Scheme 4-2.



Scheme 4-2 NaIO4 oxidation of sugars and amino acids to useful dialdehydes: a) antibody containing polysaccharide chain b) N-terminal serine peptide c) 3'-terminus of RNA.

The obtained aldehydes were originally condensed with primary amines, forming labile Schiff bases or where irreversible covalent bonds were required, reductive aminations with additional cyano borohydride were performed.[126] More modern techniques employ condensation reactions with hydroxylamines (and hydrazines or hydrazides) since the corresponding Schiff bases are significantly more stable due to the *alpha effect* (see 4.1.1.). Much effort has been put into optimizing the rate of conjugation with hydroxylamines and carbonyls, which is needed at very low concentrations for applications in chemical biology. Jencks described in his pioneering mechanistic analysis of carbonyl addition reactions[132] a two-step mechanism starting with a rapid addition of the nucleophile, forming a tetrahedral intermediate, followed by the rate limiting elimination of water. Hence, most strategies towards fast oxime formation focus on facilitation of the dehydration step. Acid catalysis was studied and applied by Jencks and it was shown that the rate of addition follows a bell shaped profile. A maximum rate is obtained at pH 4.5, below and above this optimal value slower rates are observed. This observation stems from the need of a certain amount of protons to activate the dehydration but too high concentrations also protonate the hydroxylamine, effectively decreasing its nucleophilicity. Although these fundamental results give a good insight and provide a base for basic understanding in oxime formations, they are not applicable in bioconjugation due to the need of high rate constants under physiological conditions (i.e. pH 6-8)

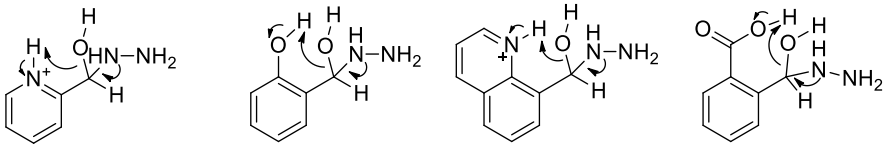
One of the current approaches is nucleophilic catalysis. Dawson showed that the addition of aniline increases the rate of ligation at pH 7 by a factor of 40, making hydroxylamine conjugations under physiological conditions possible[127]. Reaction times reaching below 30 minutes are achieved this way. Dawson attributes the increase of rate to the formation of an iminium species which undergoes subsequently rapid transimination with the hydroxylamine, forming a stable oxime (Scheme 4-3). The reason for the high activity of the intermediate imine is due to its much lower pK_a compared to the oxime and is thus protonated under the ligation conditions, featuring a much more activated carbon. This methodology was applied to conjugate a glyoxyl peptide with a hydroxylamine terminated peptide under physiological conditions at a concentration of 1 mM.



Scheme 4-3 Aniline catalyzed oxime formation via a highly activated iminium intermediate.

More recently, Distefano *et al*. employed *m*-phenylenediamine (mPDA).[133] It follows the same mechanistic principle but the rate constants were found to be about two times higher than with aniline. The major benefit of employing mPDA however, is its second amine, making its effective water solubility significantly larger (100 mM for Ph-NH_2 vs > 2 M for mPDA). Therefore a lot more catalyst can be added, leading to an increase of rate against aniline of up to 15 times at 750 mM mPDA. To ensure no side reactions at elevated concentrations, the effect of mPDA on protein structures and enzymatic function was studied and found to be benign.

Another strategy was reported by Kool.[134] A strong increase of rate was observed when condensing hydrazines with acid/base *ortho*-substituted benzaldehydes (Scheme 4-4). Although this study was not conducted with hydroxylamines but hydrazines, it provides a base for further development and delivers a concept which is likely to be applicable for oxime formations as well. It is suggested that the substituent allows for intramolecular proton donation, facilitating the rate limiting dehydration step (*vide supra*).

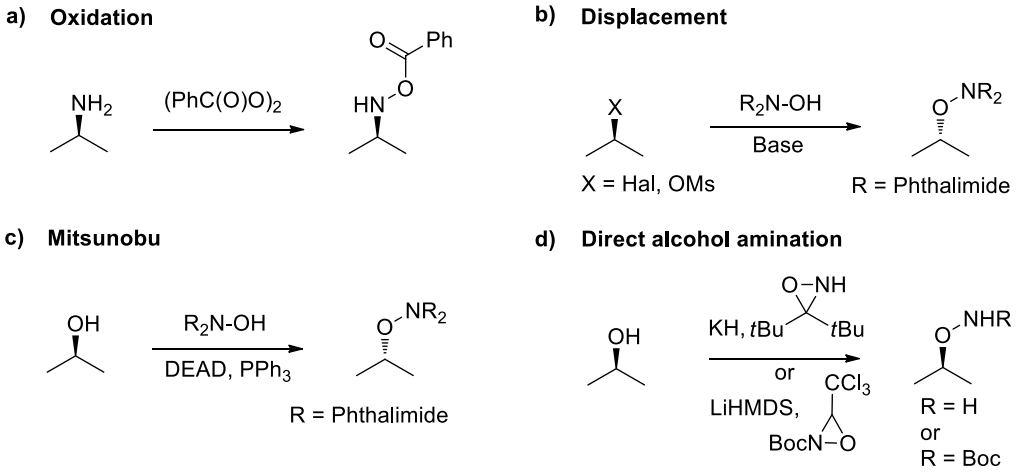


Scheme 4-4 Self catalyzing effect of *ortho*- substituted aryl aldehydes: intra molecular proton donation.

Rate constants between 0.11 and 0.16 min^{-1} were measured and indicated a rate acceleration of 2-4 folds, compared to the non *ortho*-substituted control substrates.

4.1.3 Previous syntheses

Despite their importance, methods to prepare oximes either cannot be generalized, employ hazardous intermediates and harsh conditions, or they require multi-step syntheses (Scheme 4-5). These drawbacks affect the decision making of biological researchers and medicinal chemists: for biological researchers multi-step synthesis is often a prohibitive barrier and for medicinal chemists modularity is key. There are four general approaches to alkylhydroxylamines (Scheme 4-5).

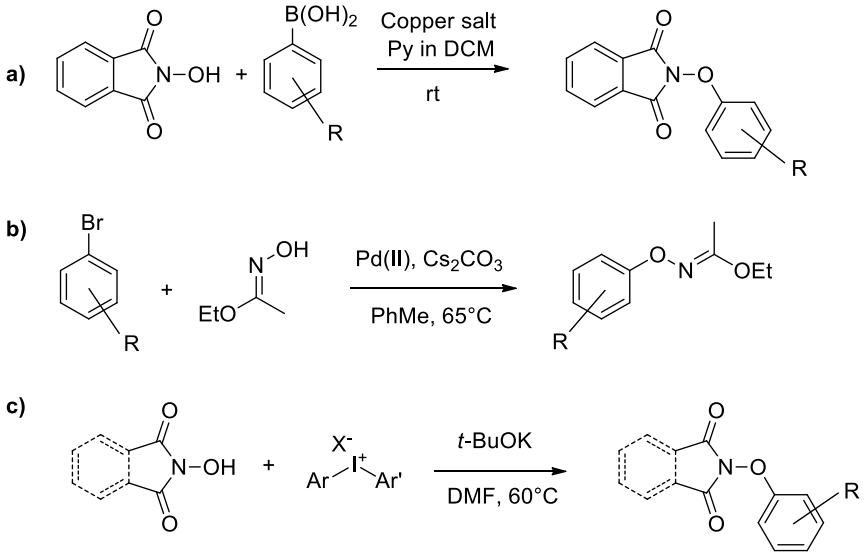


Scheme 4-5 Current transition metal free methods for non-aryl hydroxylamine synthesis.

For N-alkylated hydroxylamines oxidation with peroxides is effective[135], but these products are less valuable than O-alkylated hydroxylamines. The most common method to form O-alkylated

hydroxylamines is to displace a leaving group on an sp^3 carbon with N-hydroxyphthalimide and then perform hydrazinolysis.[136] But this approach is harsh and demands at least a three-step synthetic sequence (prepare electrophile, displace, deprotect). The Mitsunobu variation of the displacement approach obviates the need to prepare the electrophile, but product streams from Mitsonubu reactions are notoriously difficult to purify. Both of these methods lead to an inversion of configuration at the carbon and require hydrazinolysis.[137]Direct alcohol amination with electrophilic nitrogen equivalents is theoretically the most efficient approach to primary O-alkylhydroxylamines (see bottom right of Scheme 4-5); and in complex molecules, where introduction of a leaving group may not be trivial, direct amination might be the only possibility. Although two procedures that employ electrophilic nitrogen (in the form of oxaziridines) are known,[138,139] most researchers still resort to the displacement approach. The pioneering efforts to employ oxaziridines broke new ground in O-alkylhydroxylamine synthesis, but the broad adoption of these methods has been hindered by the need to prepare the reactive oxaziridines, as well as by the need for strongly basic conditions in the amination. The drawback that has prevented us from using direct amination whenever we needed hydroxylamines, however, is the low functional group compatibility of oxaziridines. Particularly for applications in bioconjugation, tolerance to a wide range of functional groups is vital.

On the other hand, milder methods are available for the synthesis of aryl hydroxylamines. A copper catalyzed introduction of phthalimide protected hydroxylamines by transmetalation of aryl boronic acids (Scheme 4-6, a) was reported by Kelly.[140]



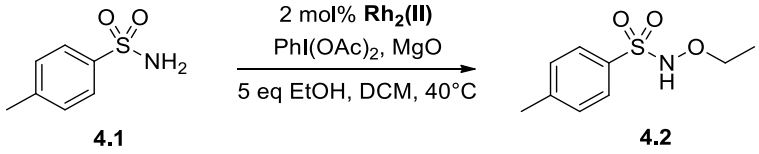
Scheme 4-6 Current methods to synthesize aryl hydroxylamines.

Although the formation of the aryl hydroxylamine is mild, aryl boronic acids are sometimes difficult to introduce and a hydrazinolysis is still necessary, limiting the usefulness of this reaction. More recently a palladium catalyzed cross coupling (Scheme 4-6, b) with aryl bromides and ethyl acetohydroximate giving oximes in good yields was published by Buchwald[141]. Mild coupling and a broad substrate scope is shown, but a rather harsh (6M HCl aq) deprotection is needed. Both methodologies employ heavy metals, which is well established in organic synthesis, but can further limit the application in chemical biology if metal traces (even after purification) interfere with e.g. bio assays. A metal free variant (Scheme 4-6, c) has beem reported by Olofsson.[142] *N*-Hydroxyphtalimide and *N*-hydroxysuccinimide were arylated with diaryliodonium salts. Although this procedure allows the synthesis of aryl hydroxylamines in excellent yields, a strong base and elevated temperature is employed. In addition, the synthesis of the aryl iodonium salts makes the application for more complex systems very difficult and thus again strongly limits the application in chemical biology. Further, a rather harsh hydrazine- or ammonolysis is required once again to obtain the requisite hydroxylamines.

4.2 Synthesis

The starting point for our study was the hypothesis that other forms of electrophilic nitrogen might prove superior to oxaziridines. We first turned to metal-stabilized nitrenes since these electrophilic nitrogen species have proven valuable in C-H amination[143] and their functional group tolerance is impressive. In preliminary experiments we were indeed pleased to find that N-tosyl O-ethylhydroxylamine **4.2** formed cleanly but in low yield by employing the Du Bois conditions for nitrene insertion (Table 4-1). As far as we can find, this is the first example of a metal-catalyzed nitrene insertion with a heteroatom.

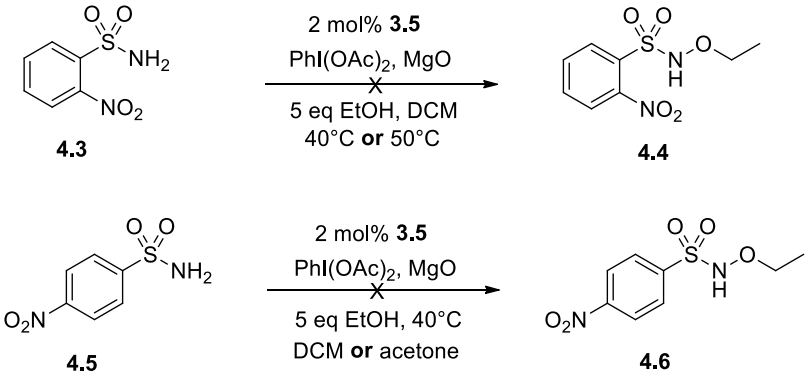
Table 4-1 Initial nitrene insertion into O-H bonds.



4.1 **4.2**

Rhodium (II)	Time [h]	Conversion of $TsNH_2$ [%]	Isolated yield **4.2** [%]
3.5	2	55	16
$Rh_2(OAc)_4$	2	30	-
$Rh_2(esp)_2$	Over night	-	-

Since unactivated tosylamides require harsh conditions to deprotect[144] this intriguing reaction would likely have little synthetic value. Unfortunately attempts to extend the substrate scope to the more synthetically valuable nosyl-amides (**4.4** and **4.6**) failed (Scheme 4-7)



4.3 **4.4**

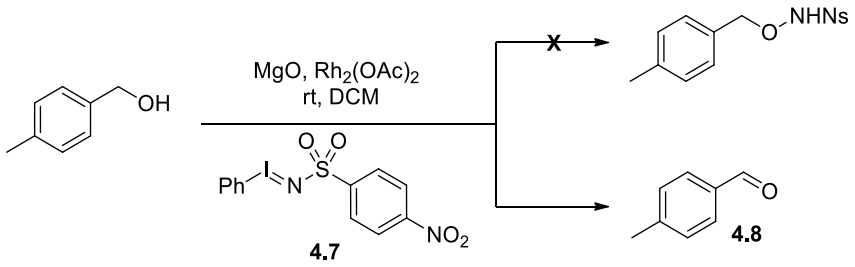
4.5 **4.6**

Scheme 4-7 Attempts towards nosyl-protected hydroxylamines by Rh(II) catalyzed nitrene insertion.

The solubility of those highly polar substrates turned out to be very low in DCM. This problem could not be resolved with increased heating in a sealed reaction flask. In the case of para-nosyl amine, changing to acetone did help to dissolve it, but still no conversion to the desired product was

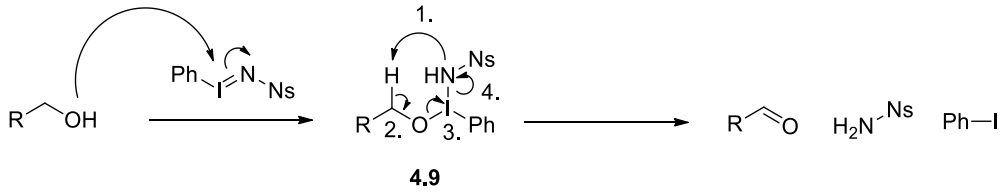
observed. We thus concluded that solubility was not necessarily the main problem, but rather that the strong electron withdrawing character of the nitro group was inhibiting the oxidation of the amine to the nitrene.

To overcome the initial and problematic *in-situ* oxidation of the sulfonamide to the nitrene by $PhI(OAc)_2$, a two-step protocol was considered. In the first step imino iodinane **4.7** was synthesized under strongly alkaline conditions according to a literature procedure and isolated in good yield[145]. In the following reaction **4.7** was converted under same conditions with a Rh(II) catalyst and MgO as a lewis acid additive, assuming that the Rh(II) would insert into the I-N bond and form a nitrene complex. This approach was already successfully employed for rhodium catalyzed C-H insertions[146] and copper catalyzed aziridine formation[147]. Very much to our surprise though, the only formed product isolated after flash chromatography was the corresponding aldehyde **4.8**. (Scheme 4-8)



Scheme 4-8 Reaction with pre-made imino iodinane gives the corresponding aldehyde.

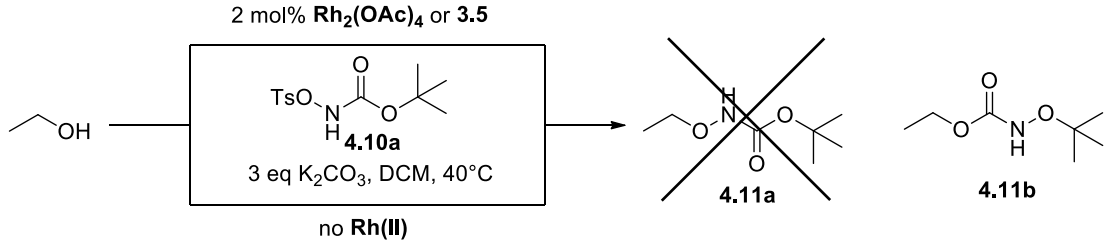
Interestingly, after only 1h stirring at room temperature, all benzylic alcohol was converted into a new product but according to 1H NMR analysis no aldehyde formed yet. It was only after flash chromatography that the aldehyde formed, which suggests a stable intermediate decomposing on silica gel. Scheme 4-9 shows the proposed intermediate **4.9** and the decomposition, affording an aldehyde.



Scheme 4-9 Proposed mechanism for the observed oxidation of alcohols to aldehydes.

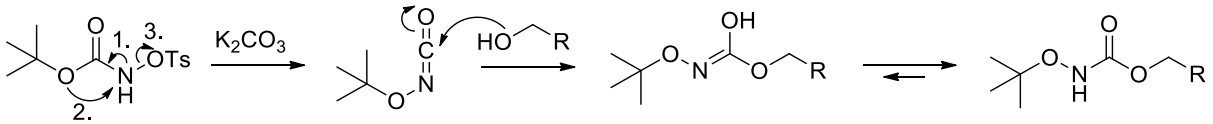
As an alternative source of nitrenes we probed *N*-*t*-butyl carbamate. Carbamates have been used extensively as nitrene precursors by Du Bois[87] and without a nitro group and a less electronegative carbon in the centre instead of sulfur, we were hoping to overcome the problems faced with nosyl amines **4.3** and **4.5.** Unfortunately, no conversion of the alcohol was observed.

Inspired by the work of Lebel we then turned to the commercially available tosylhydroxylamine **4.10a** as a nitrene[148] precursor (Scheme 4-10). Employment of $Rh_2(OAc)_4$ and **3.5** as catalyst seemed to furnish the desired N-Boc hydroxylamine **4.11a** under the conditions described by Lebel, however a closer look revealed the unprecedented formation of *N*-(*t*-butoxy)carbamate **4.11b**. DuBois' $Rh_2(esp)_2$ failed to give **4.11a** or **b**. To our surprise however, *the control reaction without Rh(II) also gave the N-(t-butoxy)carbamate*, suggesting a concerted nucleophilic substitution rather than a Rh-nitrene reaction mechanism. This proposal finds precedence in the prior use of **4.10a** to synthesize aziridines from enones,[149] probably through an S_N2 displacement at the electrophilic nitrogen atom.



Scheme 4-10 Unexpected result of the control experiment: No rhodium is needed for the synthesis and carbamates are formed.

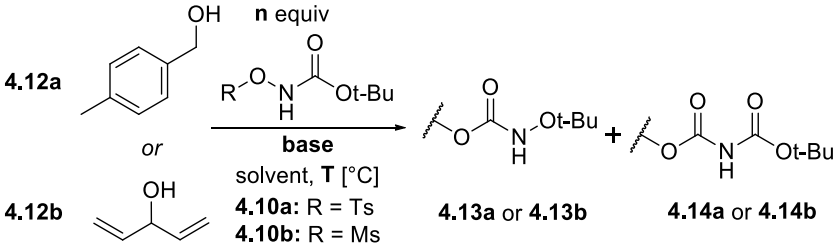
A comprehensive literature search taught us that similar electrophilic nitrogens have been used in the synthesis of *N*-(*t*-butoxy)ureas[150] but never for the synthesis of *N-(t*-butoxy)carbamates. The suggested mechanism for the formation of *N-(t*-butoxy)carbamates is shown in Scheme 4-11 featuring a Lossen rearrangement.



Scheme 4-11 Suggested mechanism of the *N*-(*t*-butoxy)carbamate foramtion via a Lossen rearrangement.

There are two reported cases of *O*-arylhydroxylamine syntheses with reagent **4.10a.**[151] The intriguing finding however, that under our conditions *N-(t*-butoxy)carbamates were obtained, motivated us to explore in detail the potential of **4.10a**.

Table 4-2 Optimization of reagent and conditions.



entry	alc.	sol.	n R	Base	T [°C]	**4.13**:**4.14**	conv.
1	**4.12a**	DCM	1 Ts	K_2CO_3	40	2:1	45%
2	**4.12a**	DMF	1 Ts	K_2CO_3	40	99:1	11%
3	**4.12a**	MeCN	1 Ts	K_2CO_3	40	5:1	16%
4	**4.12a**	EtOAc	1 Ts	K_2CO_3	40	1:5	20%
5	**4.12a**	THF	1 Ts	K_2CO_3	40	1:1	20%
6	**4.12a**	MTBE	1 Ts	K_2CO_3	40	2:1	23%
7	**4.12a**	TFT	1 Ts	K_2CO_3	40	2:1	50%
8	**4.12a**	TFT	2 Ts	K_2CO_3	40	5:2	98%
9	**4.12a**	TFT	1 Ts	Na_2CO_3	40	3:1	8%
10	**4.12a**	TFT	1 Ts	Cs_2CO_3	40	1:2	15%
11	**4.12a**	TFT	1 Ts	NEt_3	40	-	-
12	**4.12a**	TFT	1 Ms	K_2CO_3	40	5:1	57%
13	**4.12a**	TFT	1 Ms	Li_2CO_3	40	-	-
14	**4.12a**	TFT	1 Ms	Na_2CO_3	40	5:2	43%
15	**4.12a**	TFT	1 Ms	KH	rt	3:2	5%
16	**4.12b**	TFT	2 Ts	K_2CO_3	40	1:1	48%
17	**4.12b**	TFT	2 Ms	K_2CO_3	40	1:1	58%
18	**4.12b**	TFT	2 Ms	K_2CO_3	70	3:1	98%

p-Methyl benzyl alcohol (**4.12a**) was chosen as the alcohol substrate for reaction optimization for its ease of analysis (i.e. simple, easy-to-monitor NMR spectrum) and low volatility. A solvent screen (Table 4-2, entry 1-7) identified α,α,α-trifluorotoluene (TFT) as optimal (entry 7), followed closely by dichloromethane (entry 1). Employing two equivalents of reagent **4.10a** was sufficient to deliver high conversion with the primary alcohol (entry 8). While a base screen (entries 9-15) confirmed the primacy of potassium carbonate, some observations of what occurred with other bases merit mention: While sodium carbonate was simply slower (entries 9 & 14), cesium carbonate (entry 10) and NEt_3 (entry 11) led to rapid reagent decomposition. Full deprotonation of the alcohol with

potassium hydride (as is employed in oxaziridine protocols, see introduction 4.1.3) led to very poor reaction in this case. While the conditions in entry 8 provide a satisfactory protocol for primary alcohol modification, two main drawbacks led us to test some further conditions: a substantial amount of a side-product (**4.14**) that seems to stem from a rearrangement of **4.13** led to moderate isolated yields. The second problem was that reagent **4.10a** delivered only moderate conversion with secondary alcohol **4.12b** (entry 16). By switching to a mesylate leaving group (**4.10b**) both of these problems were mitigated. In the case of primary alcohol **4.12a**, comparing entries 7 and 12 highlights **4.10b**'s higher reactivity (57% vs 50% conversion) and its ability to maximize the ratio of **4.13**:**4.14** (5:1 vs 2:1). The combination of a mesylate leaving group and higher temperature also gave a solution to the reactivity problem with secondary alcohol **4.12b**. As seen in entry 18, complete conversion of **4.12b** could be achieved at 70 ˚C, with an acceptable **4.13b**:**4.14b** ratio of 3:1.

The side-product **4.14** leads to moderate yields of **4.13** (typically 40-60%, see Table 4-3) after purification. The advantage of a one-step protocol, however, should far outweigh the disadvantage of moderate yields. The structure of the side-product **4.14** was determined unambiguously by X-Ray crystallography in case of alcohol substrate **4.12f**.

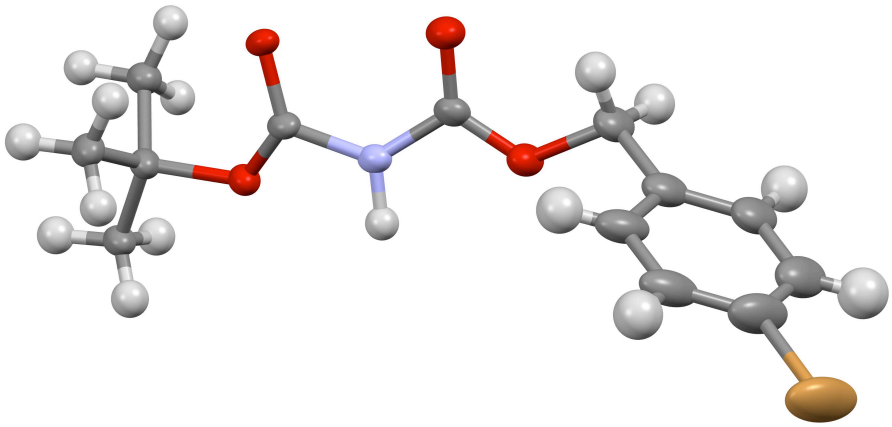
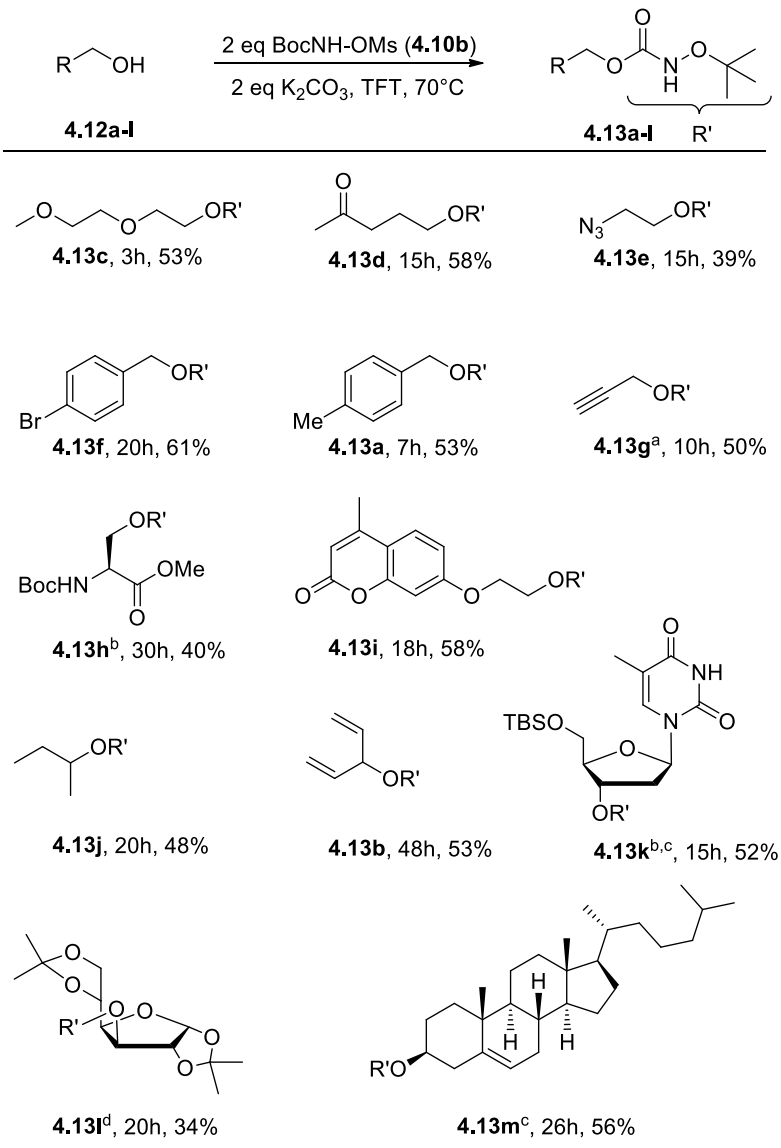


Figure 4-3 Elipsoid plot of side product 4.14f, suggesting a imidocarbonic acid. (Grey: carbon, white: hydrogen, red: oxygen, purple: nitrogen, golden: bromine)

We chose a broad swath of substrates that included functional groups and structural motifs common in chemical biology. In terms of functional groups the method tolerates: ethers, ketones, azides, esters, aryl bromides, enones, carbamates, olefins, silyl ethers, alkynes, and ketals (Table 4-3, **4.13a-m**). Within the set of primary alcohols important structural motifs include: PEG chains (**4.13c**), azide- (**4.13e**) and propargyl (**4.13g**) groups, serine (**4.13h**), and a coumarin fluorophore (**4.13i**). The ketone (**4.13d**), azide (**4.13e**), propargyl (**4.13g**) and aryl bromide (**4.13f**) offer the prospect of use in

bioconjugation. Product **4.13h** sets the stage for the synthesis of *N*-(*t*-butoxy)carbamate-bearing peptides: The modified serine derivative **4.13h** could be incorporated internally into a peptide sequence and allow for artificial functionality.

Table 4-3 Synthesized *N*-(*t*-butoxy)carbamates with reagent 4.10b.



[a]2.5 eq of K_2CO_3 were used. [b]3 equivalents of **4.10b** were used. [c]90% purity obtained with 10% contamination of the discussed sideproduct. [d]6 eq of **4.10b** and 5 eq of K_2CO_3 were used, 45% conversion obtained.

The reaction also proved general with secondary alcohols. As in the case of primary alcohols we first proved the principle with simple substrates (**4.13b** and **4.13j**) and then to demonstrate the method's

full potential we moved on to important, structurally complex motifs in chemical biology. Using the direct carbonylation approach **4.13k** could be synthesized in two steps and 48% overall yield (52% for the amination). In a further example a protected monosaccharide derivative (**4.13l**) could be prepared in 34% yield, reiterating the scope and functional group tolerance of reagent **4.10b**. Steroidal carbamate **4.13m** was prepared from cholesterol (**4.12m**) in 56% isolated yield. All alcohols shown in Table 4-3 were transformed into their corresponding *N-(t*-butoxy)carbamates in useful yields (40-60%). Depending on the functional groups and the steric environment of the substrates, reaction times between 3 and 30 h were necessary. The conversion of glucofuranose **4.12l** indicated reagent **4.10b**'s limits: Although secondary alcohols were usually converted as smooth as primary alcohols into their corresponding carbamates, the sterically crowded environment around the alcohol in **4.12l** made a big excess of reagent **4.10b** and a careful stepwise addition necessary. The resulting highly concentrated reaction mixtures became almost impossible to stir with conventional magnetic stir bar methods and only became more liquid after most of the reagent decomposed. Despite the extra efforts, not more than 45% conversion could be achieved in the case of **4.12l**.

Some substrate classes did not work (Figure 4-4): for example electron deficient alcohols such as those in hydroxy acetone or methyl glycolate were unreactive. Polarity was also observed to become an issue at some point. TFT does dissolve many substrate classes very efficiently and even rather polar substrates, like nucleotide **4.12k,** were converted in good yields, although it didn't dissolve completely from the beginning. However, the methodology reached its limits with the very polar propylene glycol. It did not dissolve in TFT leading to erratic results. Another case was ferrocenyl methanol: A bright orange solution was obtained as expected after the alcohol was added to the reagent (**4.10b**), but as soon as the base was added a rapid color change to green was observed. This indicated that the combination of reagent **4.10b** and K_2CO_3 has an oxidation potential to oxidize Fe^{2+} to Fe^{3+} and suggested that oxidation labile compounds are less suitable for the conditions shown in Table 4-3. In addition, tertiary alcohols and phenols were not converted to their corresponding *N-(t*-butoxy)carbamates. While the tertiary alcohols simply didn't undergo conversion, phenols did show an unprecedented behavior. Phenol, 4-nitro phenol and Boc-Tyr-OMe gave very quickly brownish slurries, indicating different reaction pathways than with aliphatic alcohols. ^{1}H NMR analysis showed mostly unconverted phenols, but upon reisolation only very little amounts were received.

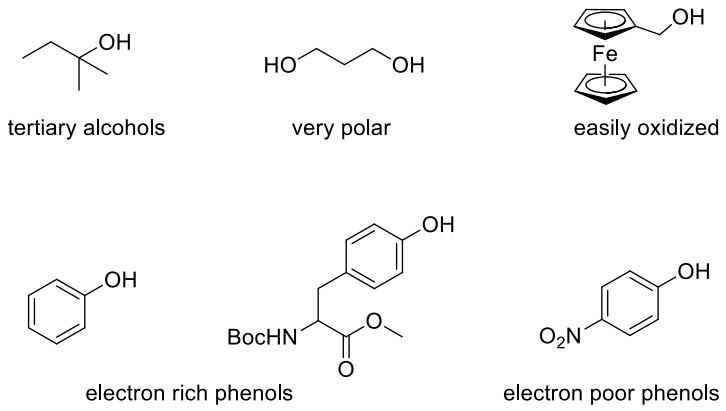
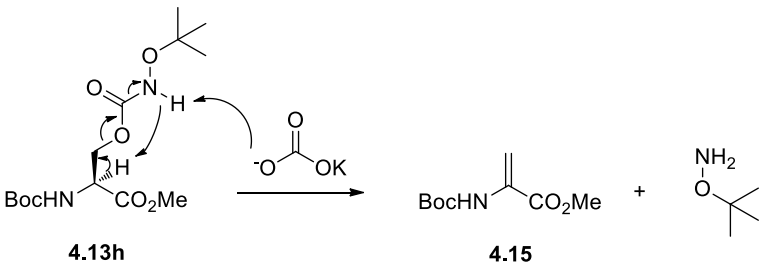


Figure 4-4 Non-compatible substrates for reactions with reagent 4.10a or 4.10b.

While running the reaction with protected serine **4.12h** for the first time, more than just the usual starting material, product and side product peaks were found in the aliquot ^{1}H NMR. A fourth signal at 3.83 ppm, suggesting another methoxy group, suggested the formation of another side product. Upon flash chromatography a UV absorbing compound eluted after only 2 column volumes and ^{1}H NMR spectra revealed it to be the second side product. After interpretation of the spectrum and comparing with literature data[152], it was concluded to be Boc-(2H)Ala-OMe **4.15.** In an attempt to minimize its formation by reduction of the reaction temperature, no difference in the roughly 1:1 ratio between **4.13h** and **4.15** was achieved.



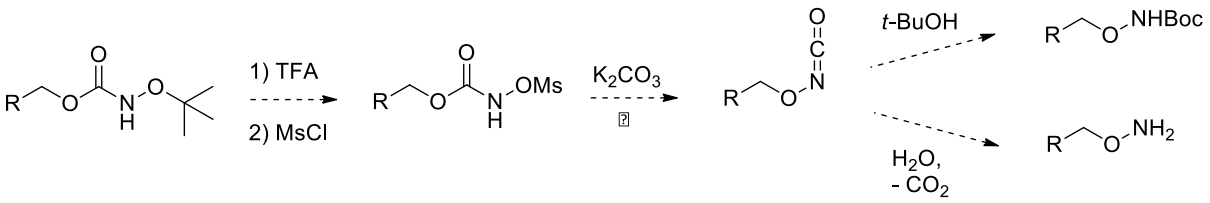
4.13h **4.15**

Scheme 4-12 proposed mechanism of the formation of dehydro alanine.

Although this made the synthesis of hydroxylamine **4.13h** slightly more problematic and lower yielding, the unintended elimination rendered carbamate **4.13h** even more interesting: the Michael acceptor in dehydro alanine is commonly used for ligation with thiols in peptide modification protocols.[153] The only plausible explanation for the formation of **4.15** is a base induced, intra molecular elimination (Scheme 4-12). This could be exploited to activate **4.13h** containing peptides towards thiol addition by simple treatment with base.

4.3 Conclusion and perspective

During the process of the development of a new methodology for alcohol amination we stumbled over what is to our knowledge the first described example of alcohols employed as nucleophiles in Lossen rearrangements. The obtained *N*-*(t*-butoxy)carbamates are less valuable at first glance than the planned *N*-Boc protected hydroxylamines, however they could be used in order to obtain the desired hydroxylamines via a multistep protocol. After an acid mediated removal of the *t*-butyl group, activation by mesylation would give again a substrate suitable for a Lossen rearrangement. By subsequent addition of *t*-butanol or water, *N*-Boc protected hydroxylamines or free *O*-alkylhydroxylamines could be obtained respectively (Scheme 4-13).



Scheme 4-13 Suggested proceeding with synthesized *N*-*(t*-butoxy)carbamates.

The unprecedented isolation of dehydroalanine **4.15** during the synthesis of serine carbamate **4.13h** provides a base for further studies with reagent **4.10b**. The suggested mechanism of a base initiated elimination should be further studied and optimized. A seminal screening with commonly employed inorganic and organic bases should quickly verify the proposed mechanism and allow for optimization of the reaction. The application of a triggered dehydroalanine synthesis on a peptide seems within reach.

5 Experimental

5.1 General

5.1.1 General Remarks, Chemicals and Equipment used

All reagents and solvents used were of analytical grade. All chemicals were purchased from Sigma-Aldrich, Alfa Aesar, Fluka, Acros, Merck, Strem, or Fluorochem and used as received if not otherwise stated. Analytical TLC was performed on silica gel 60 F_{254} pre-coated glass plates. The developed plates were examined under UV light (254 nm) or by staining with potassium permanganate followed by heating (preparation in 5.1.2). Flash chromatography was performed on silica gel 60 40-63 μm (230-400 mesh) (SiliCycle, Quebec) on a Biotage Isolera Four or with conventional glass columns. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker AvanceIII+ (500.13 MHz or 400.13 MHz proton frequency) spectrometer at 298 K. Chemical shifts (δ values) are reported in ppm, spectra were calibrated related to solvent's residual peak. Multiplicity is reported as follows: s – singlet, d – doublet, dd – doublet of doublet, t – triplet, q – quartet, quin – quintet, s br – broad singlet and coupling constant *J* in Hz. ESI-MS spectra (LRMS) were recorded on a Bruker Esquire3000+ spectrometer by direct injection in positive or negative polarity of the ion trap detector. High resolution mass spectra (HRMS) were recorded by the mass spectrometric service of the University of Basel on a Bruker maXis 4G QTOF ESI mass spectrometer. Optical rotation was measured on a Perkin Elmer polarimeter 341 using a Na/HgI lamp at 589 nm and concentrations are given in g/100 mL. Preparative HPLC was performed on a Shimadzu Prominence UFLC Fast LC system equipped with a Gemini NX5u RP18e 250 x 21.2 mm column (Phenomenex). Detection was carried out by monitoring the absorbance of the column effluent at the wavelength given below.

Reactions involving air or moisture sensitive reagents or intermediates were performed under nitrogen in glassware which was dried with a heat gun under high vacuum. Common schlenk line techniques were applied. Concentration under reduced pressure was performed by rotary evaporation at 40°C (unless otherwise specified). Amine bases were filtered through a short column of neutral Al_2O_3 Brockmann activity 1 prior to use. Dry solvents were purchased from Aldrich in sure-seal bottles, except of chloroform which was purchased from Acros. 1,4-dioxane was freshly distilled over Na/benzophenone prior to use.

5.1.2 General and useful procedures

Titration of alkyl lithium and magnesium reagents: If exact concentrations of alkyl lithium (e.g *n*-BuLi) or alkyl magnesium (isopropyl magnesium chloride) reagents were necessary, the following procedure was performed (example with *n*-BuLi). A rigorously dried 25 mL round bottom flask was purged with N_2 and then charged with 5 mL dry THF and a very small amount of 1,10-phenantroline (color indicator). Then *n*-BuLi was added until a color change was observed (to quench residual water, if perfectly dry conditions were present, the first drop led to a red-brown color immediately). 25 μL (0.27 mmol) dry sec-butanol (stored over 4A molecular sieves) was added as the species to titrate against, before the solution was cooled to 0°C. Then, *n*-BuLi was added dropwise until a colorchange was observed. The amount of *n*-BuLi used was written down and the process was restarted by addition of 25 μL (0.27 mmol) dry sec-butanol. Three titrations were performed in this way and the average concentration calculated. ([*n*-BuLi] = 0.27 mmol / added mL)

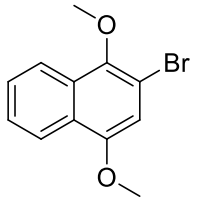
Preparation of LDA: Freshly filtered diisopropyl amine (1eq) was added to dry THF (ca 0.1 M) in a dry round bottom flask under a N_2 atmosphere and then cooled to -78°C. To the stirring solution, n-BuLi (0.95 eq, 1.6 M in hexane) was added dropwise and after completion the cooling was removed and the solution was allowed to slowly warm up to room temperature. After stirring for 2 min at room temperature, the pale yellow solution was ready to use. (Usually cooled to -78°C again for addition of the reactant)

$KMnO_4$ stain: 3 g $KMnO_4$ and 20g K_2CO_3 suspended in 5 mL aqueous 5% NaOH and then diluted with 300 mL water to obtain a deep purple solution.

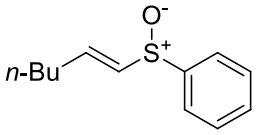
Dry loading: The crude product does often not dissolve in the solvent mixture which is required for the upcoming chromatography. A good way to solve this issue is dry-loading. Thus, the crude product was dissolved in a small amount of DCM (ca. 5 mL / 100 mg) and a spoon of silica gel was added. After some swirling, the silica gel was finely dispersed in the suspension and no lumps were visible anymore. The resulting suspension was concentrated under reduced pressure and a free flowing solid was obtained. If a sticky solid was obtained, the process was repeated and more silica gel was added. The obtained solid was poured onto the packed column and moistened with the initial gradient solvent mixture. Eventually sea sand was added on top and the elution was started.

5.2 Kinamycin and Lomaiviticin studies

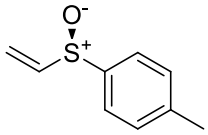
5.2.1 Reported compounds needed for the Heck methodology



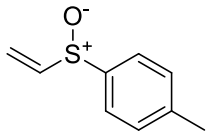
Hydroquinone 1.25 was synthesized according to De Koning.[154]



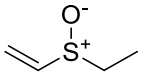
Sulfoxide 1.29 was synthesized according to Menicagli [155]



Enantiopure sulfoxide 1.31(*R*) was synthesized according to Larpent [156]

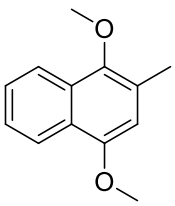


Racemic sulfoxide 1.31(*rac*) was synthesized according to Carretero [157]



Ethyl vinyl sulfoxide 1.35 was synthesized according to Harayama.[158]

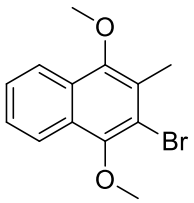
Compound **1,4-Dimethoxy-2-bromo-3-methylnaphthalene** (Table 1-3, Entry 11) was synthesized by applying Nicolaou's conditions of quinone reduction with subsequent methylation [9] and was then brominated:



1,4-Dimethoxy-2-methylnaphthalene: 1.00 g (5.81 mmol, 1.00 eq) of 2-methyl naphthoquinone was dissolved in 10 mL EtOAc, 100 mL H_2O and 100 mL Et_2O and stirred at room temperature before 7.14 g (34.9 mmol, 6.00 eq, 85% purity) $Na_2S_2O_4$ was added in one portion. The biphasic mixture stirred vigorously for 3h. Then, the layers were separated and the aqueous layer was extracted 3 times with 20 mL of EtOAc (3 x 20 ml). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The obtained solid was then dissolved in 50 mL of DMF and cooled to -10°C with an ice/NaCl cooling bath. 511 mg of NaH (12.8 mmol, 2.20 eq, 60% in mineral oil) was subsequently added in portions and the slurry stirred until no more gas evolution was observed (ca 30 min). Then, 1.45 mL of MeI (23.2 mmol, 4.00 eq) was added dropwise and the slurry stirred for 2 h before it was quenched with saturated aq. NH_4Cl solution and extracted with EtOAc (4 x 100 mL). The combined

organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure (first rotary evaporator, then high vacuum for residual DMF). After flash chromatography (3% EtOAc in cyclohexane -> 10% EtOAc in cyclohexane) 1.18 g (86%, 4.99 mmol) of the desired product was obtained as off white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.2 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.51 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.42 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 6.60 (s, 1H), 3.97 (s, 3H), 3.86 (s, 3H), 2.45 (s, 3H). Analytical data is in agreement with previously reported data.[159]

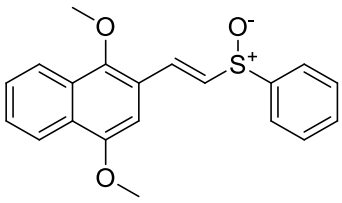


1,4-Dimethoxy-2-bromo-3-methylnaphthalene (Table 1-3, Entry 11): 200 mg (0.99 mmol, 1.00 eq) 1,4-Dimethoxy-2-methylnaphthalene were dissolved in 10 mL dry DCM, cooled to 0°C and 51 μL Br_2 (0.989 mmol, 1.00 eq) was added dropwise. The solution was stirred for 1 h at 0°C and then 2 h at room temperature. Afterwards all volatiles were removed under reduced pressure and 270 mg (99%, 0.98 mmol) of the desired product was obtained as pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 8.02 (m, 2H), 7.57 – 7.46 (m, 2H), 3.97 (s, 3H), 3.88 (s, 3H), 2.54 (s, 3H). Analytical data is in agreement with previously reported data.[160]

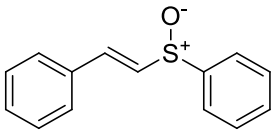
5.2.2 General procedure for the synthesis of substituted vinyl sulfoxides/sulfones/ sulfides

An oven dried, nitrogen flushed two-necked round bottom flask was charged with 5 mL of dioxane. The bromide (0.630 mmol, 1.00 eq), the sulfoxide/sulfone/sulfide (0.630 mmol, 1.00 eq), NEt_3 (1.27 mmol, 2.00 eq) and $Pd(P\mathit{t}Bu_3)_2$ (5-10 mol%, see below) was added and the mixture was immersed into a pre-heated oil bath at 70°C. The dark brown solution was stirred under a nitrogen atmosphere and the reaction was followed by NMR. As soon as the conversion stopped the solution was cooled to room temperature before removing the solvent under reduced pressure. The residue was dissolved in DCM and silica gel was added. After subsequent removal of the solvent the product laden silica was dry loaded on a column for flash chromatography. In cases where no full conversion was achieved the spare phenyl vinylsulfoxide often coeluted with the obtained products. Thus, it was removed by Kugelrohr distillation at 125°C and 0.1 mbar.



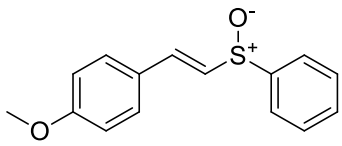
Sulfoxide 1.26 was synthesized according to the general procedure and was obtained after **3 h** with **10 mol% Pd** catalyst as a white solid (93%) after flash chromatography (10% EtOAc in cyclohexane -> 30% EtOAc in cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.18 (m, 1H), 8.11 – 8.07 (m, 1H), 7.87 (d, *J* = 15.7 Hz, 1H), 7.80 – 7.66 (m, 2H), 7.61 – 7.36 (m, 5H), 6.97 (d, *J* = 15.7 Hz, 1H), 6.73 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.29, 150.06, 144.35, 134.13, 132.58, 131.16, 129.58, 128.75, 127.95, 127.42, 127.07, 124.79, 122.78, 122.71, 121.89, 100.42, 63.43, 55.81. **HRMS** [M + Na^+] calc. for $C_{20}H_{1H}NaOS$: 361.0874, found: 361.0872.



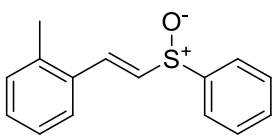
Sulfoxide 1.27a was synthesized according to the general procedure and was obtained after **0.5 h** with **5 mol% Pd** catalyst as a yellowish solid (82%) after flash chromatography (30% EtOAc in cyclohexane -> 40% EtOAc in cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.65 (m, 2H), 7.55 – 7.43 (m, 5H), 7.42 – 7.34 (m, 4H), 6.83 (d, *J* = 15.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.10, 136.57, 133.88, 133.12, 131.32, 130.03, 129.62, 129.07, 127.95, 124.89. **HRMS** [M + Na]$^+$: calc. for $C_{14}H_{12}NaOS$: 251.0506, found: 251.0501. In agreement with the side product **1.24**.[20]



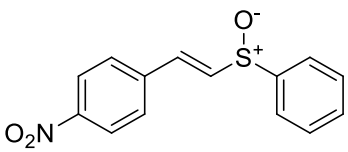
Sulfoxide 1.27b was synthesized according to the general procedure and was obtained after **2 h** with **10 mol% Pd** catalyst as a white solid (73%) after flash chromatography (20% EtOAc in cyclohexane -> 45% EtOAc in cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.65 (m, 2H), 7.55 – 7.47 (m, 3H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 15.5 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.69 (d, *J* = 15.5 Hz, 1H), 3.82 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.20, 144.46, 137.09, 131.11, 130.55, 129.55, 129.52, 126.54, 124.80, 114.46, 55.52. **HRMS** [M + Na^+] calc. for $C_{15}H_{14}NaO_2S$: 281.0612, found: 281.0607.



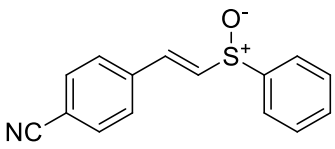
Sulfoxide 1.27c was synthesized according to the general procedure and was obtained after **2 h** with **5 mol% Pd** catalyst as a white solid (80%) after flash chromatography (15% EtOAc in cyclohexane -> 40% EtOAc in cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.67 (m, 2H), 7.64 (d, *J* = 15.4 Hz, 1H), 7.56 – 7.48 (m, 3H), 7.43 – 7.38 (m, 1H), 7.25 – 7.15 (m, 3H), 6.76 (d, *J* = 15.4 Hz, 1H), 2.46 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.96, 137.03, 134.27, 134.12, 132.69, 131.13, 130.81, 129.67, 129.46, 126.55, 126.32, 124.71, 19.81. **HRMS** [M + Na^+] calc. for C15H14NaOS: 265.0663, found: 265.0658.



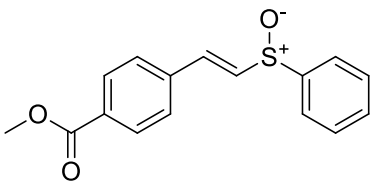
Sulfoxide 1.27d was synthesized according to the general procedure and was obtained after **1 h** with **10 mol% Pd** catalyst as a yellow solid (76%) after flash chromatography (20% EtOAc in cyclohexane -> 40% EtOAc in cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.8 Hz, 2H), 7.73 – 7.66 (m, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.57 – 7.51 (m, 3H), 7.43 (d, *J* = 15.4 Hz, 1H), 7.01 (d, *J* = 15.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.18, 143.05, 140.00, 137.84, 132.32, 131.78, 129.84, 128.49, 124.90, 124.31. **HRMS** [M + Na^+] calc. for $C_{14}H_{11}NNaO_3S$: 296.0357, found: 296.0352.



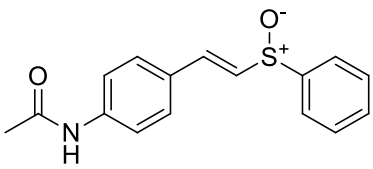
Sulfoxide 1.27e was synthesized according to the general procedure and was obtained after **2 h** with **10 mol% Pd** catalyst as a pale yellow solid (80%) after flash chromatography (30% EtOAc in cyclohexane -> 45% EtOAc in cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.62 (m, 4H), 7.58 – 7.51 (m, 5H), 7.38 (d, *J* = 15.4 Hz, 1H), 6.96 (d, *J* = 15.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.19, 138.18, 137.04, 132.98, 132.82, 131.78, 129.85, 128.31, 124.93, 118.48, 113.03. **HRMS** [M + Na^+] calc. for $C_{15}H_{11}NNaOS$: 276.0458, found: 276.0454.



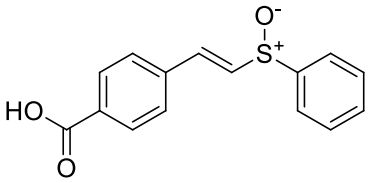
Sulfoxide 1.27f was synthesized according to the general procedure and was obtained after **2 h** with **10 mol% Pd** catalyst as an off-white solid (88%) after flash chromatography (20% EtOAc in cyclohexane -> 30% EtOAc in cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 8.00 (m, 2H), 7.71– 7.67 (m, 2H), 7.57 – 7.48 (m, 5H), 7.40 (d, *J* = 15.5 Hz, 1H), 6.93 (d, *J* = 15.4 Hz, 1H), 3.92 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.44, 143.52, 138.02, 135.64, 134.30, 131.48, 130.98, 130.20, 129.67, 127.71, 124.83, 52.32. **HRMS** [M + Na^+] calc. for $C_{16}H_{14}NaOS$: 309.0561, found: 309.0556.



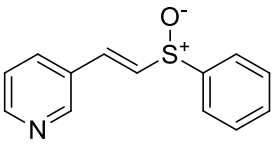
Sulfoxide 1.27g was synthesized according to the general procedure and was obtained after **2 h** with **10 mol% Pd** catalyst as a white powder (80%) after flash chromatography (60% EtOAc in cyclohexane -> 95% EtOAc in cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.70 – 7.63 (m, 2H), 7.58 – 7.47 (m, 5H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 15.5 Hz, 1H), 6.71 (d, *J* = 15.4 Hz, 1H), 2.18 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.84, 143.91, 139.96, 137.07, 131.49, 131.34, 129.63, 129.26, 128.80, 124.81, 119.99, 24.75. **HRMS** [M + Na^+] calc. for $C_{16}H_{15}NNaO_2S$: 308.0710, found: 308.0716.



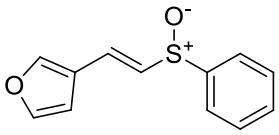
Sulfoxide 1.27h was synthesized according to the general procedure and was obtained after **2 h** with **10 mol% Pd** catalyst and **4 eq of NEt_3** as a white powder (58%) after flash chromatography (30% EtOAc in cyclohexane -> 60% EtOAc in cyclohexane, silica gel prepared with 10% AcOH in the eluent).

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.07 (s, 1H), 7.93 (d, *J* = 8.5 Hz, 2H), 7.77 – 7.69 (m, 4H), 7.65 – 7.54 (m, 4H), 7.34 (d, *J* = 15.4 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 166.81, 143.76, 137.80, 136.68, 132.77, 131.29, 131.14, 129.76, 129.61, 127.99, 124.48. **HRMS** [M + Na^+] calc. for $C_{15}H_{12}NaO_3S$: 295.0404, found: 295.0399.



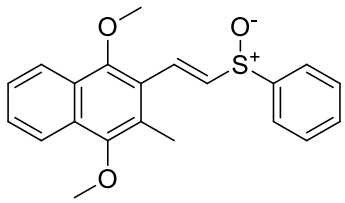
Sulfoxide 1.27i was synthesized according to the general procedure and was obtained after **40 h** with **10 mol% Pd** catalyst as a white solid (88%) after flash chromatography (50% EtOAc in cyclohexane -> 85% EtOAc in cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 1.8 Hz, 1H), 8.57 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.74 (dt, *J* = 8.0 Hz, 1.9 Hz, 1H), 7.68 (d, *J* = 1.6 Hz, 2H), 7.57 – 7.51 (m, 3H), 7.38 (d, *J* = 15.5 Hz, 1H), 7.30 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.93 (d, *J* = 15.5 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.60, 149.32, 143.39, 135.29, 134.27, 131.94, 131.58, 129.72, 129.69, 124.83, 123.80. **HRMS** [M + H^+] : calc. for $C_{13}H_{11}NOS$: 230.0561, found: 230.0634.



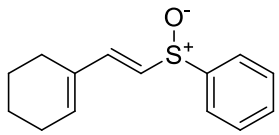
Sulfoxide 1.27j was synthesized according to the general procedure and was obtained after **24 h** with **10 mol% Pd** catalyst as a brownish oil (37%) after flash chromatography (20% EtOAc in cyclohexane -> 25% EtOAc in cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.64 (m, 2H), 7.62 (s br, 1H), 7.55 – 7.47 (m, 3H), 7.40 – 7.38 (m, 1H), 7.27 (d, *J* = 15.3 Hz, 1H), 6.57 (d, *J* = 15.3 Hz, 1H), 6.48 – 6.47 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.45, 144.18, 143.79, 132.41, 131.21, 129.54, 127.23, 124.77, 121.72, 107.69. **HRMS** [M + Na^+]: calc. for $C_{12}H_{10}NaO_2S$: 241.0299, found: 241.0294.

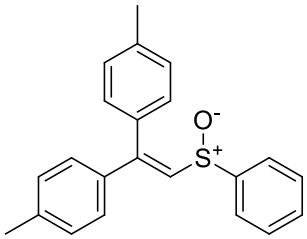


Sulfoxide 1.27k was synthesized according to the general procedure and was obtained after **1 h** with **10 mol% Pd** catalyst as a white solid (69%) after flash chromatography (10% EtOAc in cyclohexane -> 30% EtOAc in cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 8.00 (m, 2H), 7.76 – 7.70 (m, 2H), 7.60– 7.45 (m, 6H), 7.23 (d, *J* = 15.5 Hz, 1H), 3.86 (s, 3H), 3.65 (s, 3H), 2.49 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.89, 150.40, 144.21, 138.77, 131.23, 129.59, 129.21, 129.16, 127.52, 127.28, 126.12, 125.91, 124.76, 123.80, 123.00, 122.39, 61.62, 61.22, 13.60. **HRMS** [M + Na^+]: calc. for $C_{21}H_{20}NaO_3S$: 375.1030, found: 375.1025.

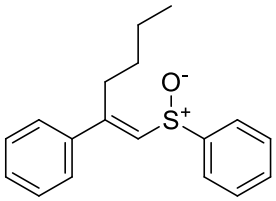


Sulfoxide 1.27l was synthesized according to the general procedure and was obtained after **6 h** with **5 mol% Pd** catalyst as a colorless oil (23%) after flash chromatography (15% EtOAc in cyclohexane -> 35% EtOAc in cyclohexane). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 – 7.60 (m, 2H), 7.53 – 7.44 (m, 3H), 6.98 (d, *J* = 15.3 Hz, 1H), 6.19 (d, *J* = 15.3 Hz, 1H), 6.14 (t, *J* = 4.0 Hz, 1H), 2.24 – 2.15 (m, 2H), 2.11 – 1.99 (m, 2H), 1.69 – 1.53 (m, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.76, 141.44, 137.76, 133.95, 130.89, 129.41, 129.40, 124.66, 26.38, 24.41, 22.05 (2C). **HRMS** [M + H^+] calc. for $C_{14}H_{16}OS$: 233.1000, found: 233.0995.



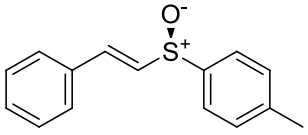
Sulfoxide 1.28 was synthesized according to the general procedure at **100°C**, **4 eq of NEt_3** and was obtained after **11 h** with **10 mol% Pd** catalyst as colorless oil after flash chromatography (cyclohexane -> 25% EtOAc in cyclohexane) containing 20 mol% single-addition product. It was not possible to push the reaction to full conversion and the two obtained products couldn't be separated. However, it was possible to obtain a single fraction after column chromatography with pure desired double-addition product, which was used for complete characterization.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.50 (m, 5H), 7.49 – 7.34 (m, 4H), 7.13 – 7.00 (m, 4H), 6.65 (s, 1H), 2.36 (s, 3H), 2.27 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.06, 145.58, 140.18, 139.36, 136.58, 134.39, 132.50, 130.75, 130.33, 129.42, 129.32, 129.22, 128.54, 124.72, 21.53, 21.40. **HRMS** [M + H^+] calc. for $C_{22}H_{21}OS$: 333.1313, found: 333.1308.



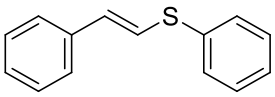
Sulfoxide 1.30 was synthesized according to the general procedure and was obtained after **21 h** with **5 mol% Pd** catalyst as colorless oil (50%) after flash chromatography (5% EtOAc in cyclohexane -> 35% EtOAc in cyclohexane). The crude mixture was heated to 130°C for 1 h at 0.4 mbar prior to chromatography in order to remove the non-converted sulfoxide **1.29**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.65 (m, 2H), 7.55 – 7.44 (m, 3H), 7.40 – 7.33 (m, 5H), 6.41 (s, 1H), 3.11 – 3.00 (m, 2H), 1.57 – 1.37 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.91, 145.08, 138.89, 133.59, 130.76, 129.46, 129.36, 128.80, 126.85, 124.38, 31.53, 31.30, 22.70, 13.95. **HRMS** [M + H^+] calc. for $C_{18}H_{21}OS$: 285.1313, found: 285.1307.



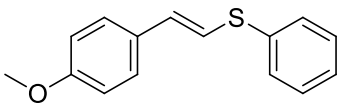
Enenantiopure sulfoxide 1.32 (*R*) was synthesized according to the general procedure and was obtained after **1.5 h** with **5 mol% Pd** catalyst as orange oil (90%) after flash chromatography (25% EtOAc in cyclohexane -> 35% EtOAc in cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.2 Hz, 2 H), 7.47 – 7.43 (m, 2 H), 7.39 – 7.29 (m, 6H), 6.81 (d, *J* = 15.5 Hz, 1H), 2.41 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.94, 140.86, 136.17, 133.97, 133.23, 130.32, 129.92, 129.05, 127.92, 125.09, 21.59. **HRMS** [M + Na^+] calc. for $C_{15}H_{14}NaOS$: 265.0662, found: 265.0658. HPLC (Daicel Chiracel IC, heptane/*i*PrOH 70:30, 0.5 mL/min, 25°C): t_R (*S*) = 36.6 min, t_R (*R*) = 42.5 min.



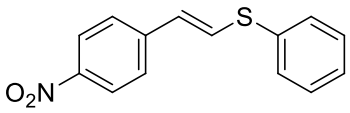
Sulfide 1.33a was synthesized according to the general procedure and was obtained after **3 h** with **10 mol% Pd** catalyst as colorless oil (73%) after flash chromatography (cyclohexane -> 5% EtOAc in cyclohexane). A formed by-product couldn't be removed completely. Else, the obtained spectra are identical to the ones reported by Venkataraman [161].

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.40 (m, 2H), 7.37 – 7.20 (m, 8H), 6.89 (d, *J* = 16 Hz, 1H), 6.74 (d, *J* = 16 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.67, 135.37, 131.95, 129.98, 129.30, 128.83, 127.73, 127.10, 126.17, 123.54.



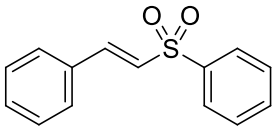
Sulfide 1.33b was synthesized according to the general procedure and was obtained after **2 h** with **10 mol% Pd** catalyst as white solid (68%) after flash chromatography with minor impurities (cyclohexane -> 4% EtOAc in cyclohexane). A pure analytical sample for characterization was obtained by preparative HPLC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 2H), 7.36 – 7.28 (m, 4H), 7.23 (ddd, *J* = 6.4, 3.9, 1.3 Hz, 1H), 6.89 – 6.82 (m, 2H), 6.76 (d, *J* = 15.4 Hz, 1H), 6.71 (d, *J* = 15.4 Hz, 1H), 3.82 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.52, 136.08, 132.88, 129.53, 129.40, 129.22, 127.52, 126.74, 120.22, 114.28, 55.48. In agreement with[162].



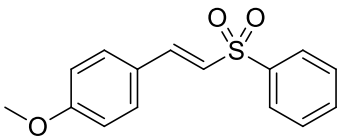
Sulfide 1.33c was synthesized according to the general procedure and was obtained after **2 h** with **10 mol% Pd** catalyst as yellow solid (68%) after flash chromatography with minor impurities (cyclohexane -> 6% EtOAc in cyclohexane). A pure analytical sample for characterization was obtained by preparative HPLC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.06 (m, 2H), 7.57 – 7.45 (m, 2H), 7.44 – 7.33 (m, 5H), 7.15 (d, *J* = 15.5 Hz, 1H), 6.57 (d, *J* = 15.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.53, 143.06, 133.13, 131.63, 131.44, 129.65, 128.34, 126.39, 126.19, 124.34. **HRMS** [M + Na^+] calc. for $C_{14}H_{11}NNaO_2S$: 280.0408, found: 280.0405



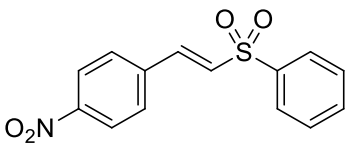
Sulfone 1.34a was synthesized according to the general procedure and was obtained after **3 h** with **5 mol% Pd** catalyst as white solid (88%) after flash chromatography (10% EtOAc in cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.93 (m, 2H), 7.69 (d, *J* = 15.4 Hz, 1H), 7.65 – 7.60 (m, 1H), 7.58 – 7.52 (m, 2H), 7.51 – 7.47 (m, 2H), 7.44 – 7.37 (m, 3H), 6.86 (d, *J* = 15.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.65, 140.88, 133.53, 132.52, 131.37, 129.49, 129.25, 128.73, 127.81, 127.44. **HRMS** [M + Na]$^+$: calc. for $C_{14}H_{12}NaO_2S$: 267.0455, found: 267.0450.



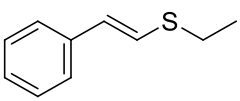
Sulfone 1.34b was synthesized according to the general procedure and was obtained after **2 h** with **10 mol% Pd** catalyst as pale yellow oil (92%, 95% purity) after flash chromatography (10% EtOAc in cyclohexane -> 20% EtOAC in cyclohexane). A pure analytical sample for characterization was obtained by preparative HPLC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.83 (m, 2H), 7.63 (d, *J* = 15.3 Hz, 1H), 7.60 – 7.49 (m, 3H), 7.42 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 15.3 Hz, 1H), 3.82 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.18, 142.40, 141.25, 133.27, 130.48, 129.37, 127.59, 125.05, 124.52, 114.62, 55.54. In agreement with[163].



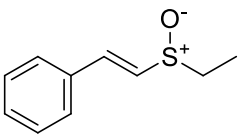
Sulfone 1.34c was synthesized according to the general procedure and was obtained after **4 h** with **10 mol% Pd** catalyst as white solid (74%) after flash chromatography (10% EtOAc in cyclohexane -> 25% EtOAc in cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.8 Hz, 2H), 8.04 – 7.85 (m, 2H), 7.72 (d, *J* = 15.5 Hz, 1H), 7.68 – 7.63 (m, 3H), 7.62 – 7.53 (m, 2H), 7.02 (d, *J* = 15.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.12, 139.90, 139.36, 138.52, 134.06, 131.85, 129.69, 129.39, 128.05, 124.42. **HRMS** [M + Na]$^+$: calc. for $C_{14}H_{11}NNaO_4S$: 312.0306, found: 312.0301



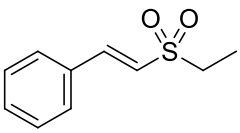
Alkyl sulfide 1.36 was synthesized according to the general procedure and was obtained after **1 h** with **5 mol% Pd** catalyst as colorless oil (81%) after flash chromatography (cyclohexane -> 5% EtOAc in cyclohexane). Small amounts of the Z-isomer are observed in the ^{1}H NMR [characteristic doublets at 6.48 (d, *J* = 10.9 Hz, 1H), 6.28 (d, *J* = 10.9 Hz, 1H)].

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 4H), 7.23 – 7.18 (m, 1H), 6.75 (d, *J* = 15.6 Hz, 1H), 6.49 (d, *J* = 15.6 Hz, 1H), 2.85 (q, *J* = 7.4 Hz, 1H), 1.38 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.18, 128.67, 126.92, 126.84, 125.50, 124.94, 26.61, 14.64. In agreement with [164].



Alkyl sulfoxide 1.37 was synthesized according to the general procedure and was obtained after **1 h** with **5 mol% Pd** catalyst as colorless oil (78%) after flash chromatography (50% EtOAc in cyclohexane -> 70% EtOAc in cyclohexane).

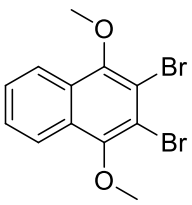
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.44 (m, 2H), 7.42 – 7.32 (m, 3H), 7.23 (d, *J* = 15.5 Hz, 1H), 6.79 (d, *J* = 15.5 Hz, 1H), 2.91 (dq, *J* = 13.3, 7.5 Hz, 1H), 2.76 (dq, *J* = 13.3, 7.4 Hz, 1H), 1.31 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.38, 133.96, 129.97, 129.76, 129.04, 127.70, 47.40, 6.06. In agreement with[165].



Alkyl sulfone 1.38 was synthesized according to the general procedure and was obtained after **4.5 h** with **5 mol% Pd** catalyst as white solid (83%) after flash chromatography (10% EtOAc in cyclohexane -> 20% EtOAc in cyclohexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 15.5 Hz, 1H), 7.51 (d, *J* = 2.3 Hz, 2H), 7.44 (t, *J* = 4.4 Hz, 3H), 6.81 (d, *J* = 15.5 Hz, 1H), 3.09 (d, *J* = 7.5 Hz, 2H), 1.39 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.34, 132.38, 131.51, 129.29, 128.70, 124.13, 49.57, 7.40. In agreement with[164].

5.2.3 Syntheses towards kinamycin and lomaiviticin

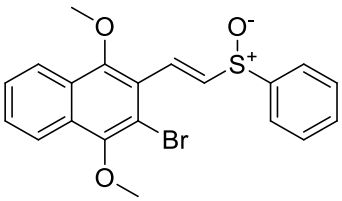


Methyl hydroquinone 1.39: A round bottom flask was charged with 4.25 g (13 mmol, 1 eq) 2,3-dibromonaphthoquinone and was subsequently dissolved in 20 mL EtOAc, 200 mL Et_2O and 200 mL H_2O. Then, 22.04 g (108 mmol, 8 eq, 85% purity, technical grade) sodium dithionite ($Na_2S_2O_4$) was added in one scoop. The resulting yellow emulsion was stirred at room temperature for 1h. After separation of the layers, the aqueous fraction was extracted three times with 100 mL EtOAc. The combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 3.6 g (10.9 mmol, 84%) crude 2,3-dibromonaphthohydroquinone as a brownish solid.

The crude material was transferred into a 250 mL flask (if not already there) and was then once coevaporated with 100 mL of benzene before it was dissolved in 120 mL dry DMF under a N_2 atmosphere and was cooled to -15°C with an ice/salt bath while stirring. Then, 1 g (25 mmol, 2.2 eq, 60% in mineral oil) was added in three equal portions while stirring and the mixture was kept at -15°C for 20 minutes (until most of the H_2 formation ceased). 2.82 mL (6.42 g, 45 mmol, 4 eq) MeI was subsequently added via syringe over 5 minutes. The cooling was removed and the slurry stirred for 4 h at room temperature before an equal amount of water was added. A precipitate formed which was filtered off and dried under reduced pressure to give 3.31 g of crude **1.39**. Purification by flash chromatography (5%, EtOAc in cyclohexane, 100 g silica, 254 nm) gave 3.91 g (76%, 8.36 mmol) of dimethyl hydroquinone **1.39** as colorless crystals.

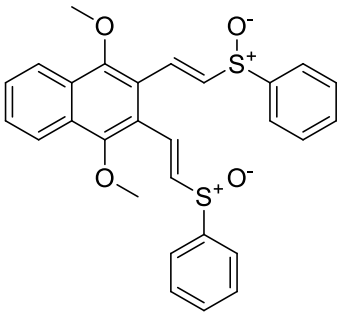
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.05 (m, 2H), 7.63 – 7.53 (m, 2H), 3.99 (s, 6H).

Analytical data is in agreement with the previously reported by Brandt.[166]



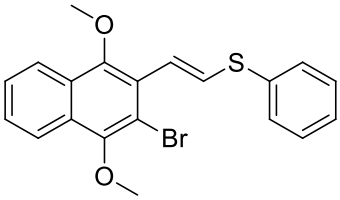
Vinyl sulfoxide 1.40: A dry round bottom flask under a N_2 atmosphere was charged with 34 mL dry and degassed toluene, before 2.27 g (6.57 mmol, 5 eq) methyl hydroquinone **1.39** and 176 μL (200 mg, 1.31 mmol, 1 eq) phenyl vinylsulfoxide was added. Then, 367 μL (266 mg, 2.62 mmol, 2 eq) NEt_3 was added, followed by 101 mg (0.2 mmol, 0.15 eq) $Pd(PtBu_3)_2$. The stirring solution was immediately immersed into a preheated oil bath at 60°C and stirred for 4 h. After allowing the brown mixture to cool to room temperature, all volatiles were removed under reduced pressure and redissolved in some DCM to add silica gel in order to dry load it on an Isolera column. After chromatography (10% EtOAc in cyclohexane -> 30% EtOAc in cyclohexane over 14 CV, 100 g SiOH, 254 nm. Excess **1.39** eluted after 1 CV, desired product **1.40** eluted after 7-9 CV) 380 mg (69%, 4.53 mmol) of sulfoxide **1.40** was obtained as yellow oil, which solidified upon standing.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 – 8.02 (m, 2H), 7.76 – 7.73 (m, 2H), 7.72 (d, *J* = 15.5 Hz, 1H), 7.59 – 7.48 (m, 5H), 7.35 (d, *J* = 15.5 Hz, 1H), 3.97 (s, 3H), 3.66 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.54, 150.56, 144.00, 140.05, 131.28, 130.46, 129.60, 129.23, 128.24, 128.14, 127.32, 124.87, 123.54, 123.36, 122.72, 115.20, 61.52, 61.38. **HRMS** [$M+H^+$] calc. for $C_{20}H_{18}BrO_3S$: 417.0155, found: 417.0152.



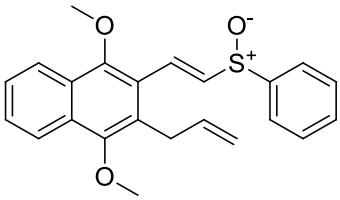
If only 1 eq of **1.39** was employed, **double Heck adduct 1.40a** was predominantly isolated (10% EtOAc in cyclohexane -> 30% EtOAc in cyclohexane over 13 CV, then 100% EtOAc 8 CV, SiOH, 254 nm. Eluted after 13 CV).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 – 8.05 (m, 2H), 7.73 – 7.69 (m, 4H), 7.60 – 7.49 (m, 10H), 7.06 (d, *J* = 15.6 Hz, 1H), 7.04 (d, *J* = 15.6 Hz, 1H), 3.70 (s, 3H), 3.69 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.86, 151.84, 143.93, 140.35, 140.34, 131.32, 129.72, 129.69, 129.06, 128.97, 127.80, 124.65, 124.58, 123.19, 122.89, 122.87, 61.64, 61.61. **HRMS** [M+H$^+$] calc. for $C_{28}H_{25}O_4S_2$: 489.1189, found: 489.1189.



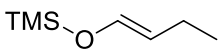
Sulfide 1.41: A flame dried round bottom flask under a N_2 atmosphere was charged with 1.8 mg (13.4 μmol, 0.2 eq) dry $NiCl_2$ and with 41 mg (335 μmol, 5 eq) dry $CrCl_2$ before the flask was dried with a heat gun and under vacuum again. After cooling to room temperature, 28 mg (67.1 μmol, 1 eq) hydroquinone **1.40** was added as a solution in benzene and all volatiles were subsequently removed under reduced pressure. Then, 3 mL of dry and degassed DMF was added, followed by 11 μL (9.7 mg, 101 μmol, 1.5 eq) sorbaldehyde via Hamilton syringe. The slurry stirred vigorously at room temperature for 20 min before it was immersed into a preheated 40°C oil bath and stirred overnight. Then, an excess of water was added and the mixture was concentrated under reduced pressure. The solids were subsequently dissolved in a small amount of DCM to mix with silica gel and dry load for column chromatography with the Isolera (10% EtOAc in cyclohexane -> 35% EtOAc in cyclohexane over 14 CV, 25 g SiOH, 254 nm, eluted after 2 CV), giving 11 mg (41%, 27.5 μmol) of sulfide **1.41** as almost colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 – 8.05 (m, 2H), 7.57 – 7.49 (m, 4H), 7.44 (d, *J* = 15.6 Hz, 1H), 7.40 – 7.36 (m, 2H), 7.32 – 7.28 (m, 1H), 6.94 (d, *J* = 15.6 Hz, 1H), 3.97 (s, 3H), 3.85 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.93, 150.26, 134.70, 131.73, 130.51, 129.38, 128.43, 128.04, 127.36, 127.13, 127.03, 125.88, 125.14, 123.03, 122.59, 115.37, 61.43, 60.90. **LRMS** (FAB) calc. for $C_{20}H_{17}BrO_2S$: 400.0, found: 400.0.

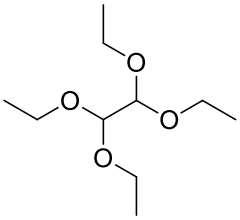


Allyl hydroquinone 1.42: A dry round bottom flask under a N_2 atmosphere was charged with 35 mg (84 μmol, 1 eq) sulfoxide **1.40** and then dissolved in 1 mL dry toluene. Then 26 μL (28 mg, 83.9 μmol, 1 eq) allyl tributylstannane was added via Hamilton syringe, followed by 4.2 mg (8.39 μmol, 0.1 eq) $Pd(PtBu_3)_2$. The solution was immersed into a preheated oil bath at 70°C and stirred for 2.5 h before it was allowed to cool to room temperature. All volatiles were removed under reduced pressure and the residue was dry loaded to purify by flash chromatography with the Isolera (10% EtOAc in cyclohexane -> 25% EtOAc in cyclohexane over 14 CV, 25 g SiOH, 254 nm, eluted after 10 CV), giving 13 mg (41%, 34.4 μmol) ally hydroquinone **1.42** as yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.02 (m, 2H), 7.73 – 7.68 (m, 2H), 7.57 – 7.46 (m, 6H), 7.27 (d, *J* = 15.5 Hz, 1H), 6.05 (ddt, *J* = 17.2, 10.5, 5.4 Hz, 1H), 5.10 (dq, *J* = 10.2, 1.7 Hz, 1H), 4.92 (dq, *J* = 17.2, 1.8 Hz, 1H), 3.89 (s, 3H), 3.72 (ddd, *J* = 5.4, 3.5, 1.7 Hz, 1H), 3.66 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.13, 150.69, 144.23, 138.94, 136.66, 131.17, 129.52, 129.32, 129.13, 128.14, 127.49, 127.26, 126.41, 124.78, 123.59, 123.10, 122.66, 116.48, 62.62, 61.17, 31.07. **HRMS** [M+H$^+$] calc. for $C_{23}H_{23}O_3S$: 379.1362, found: 379.1358.

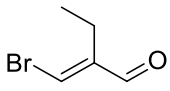


Silyl enol ether 1.43 was prepared according to a literature procedure by Warren.[167]

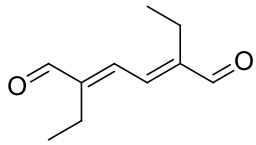


Diacetal 1.44 was synthesized according to Barnes[168] with modifications: A round bottom flask was charged with 3.5 g (24 mmol, 1 eq) 40% glyoxal in water and was suspended in 250 mL benzene. Then 5.63 mL (4.45 g, 96 mmol, 4 eq) EtOH and 92 mg (0.48 mmol, 0.02 eq) PTSA were added and the emulsion was refluxed at 95°C for 25h with a Dean-Stark trap attached. Upon cooling to room temperature, all volatiles were removed under reduced pressure and the remains were distilled: Fraction 1 at 50-70°C, 0.4 mbar gave 437 mg of ca 90% pure **1.44**, fraction 2 at 70-100°C, 0.4 mbar gave 445 mg (9%, 2.15 mmol) of pure product **1.44.**

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (s, 2H), 3.72 (dq, *J* = 9.4, 7.1 Hz, 4H), 3.63 (dq, *J* = 9.4, 7.1 Hz, 4H), 1.22 (t, *J* = 7.1 Hz, 12H).



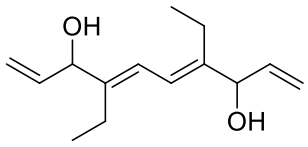
Bromoacrolein 1.45 was prepared according to a literature procedure by Hoveyda.[169]



Dialdehyde 1.46: A dry round bottom flask under a N_2 atmosphere was charged with 3.41 g (12 mmol, 1 eq) TBAC, 2.58 g (31 mmol, 2.5 eq) $NaHCO_3$ and 275 mg (1.2 mmol, 0.1 eq) $Pd(OAc)_2$, which were suspended in 20 mL dry DMF. Then, three freeze pump thaw cycles were done, before 2 g (12 mmol, 1 eq) **1.45** and 2.86 mL (2.43 g, 25 mmol, 2 eq) 2-ethylacrolein were added. The reaction mixture stirred overnight and all the DMF was then removed under reduced pressure. The remainings were dissolved in DCM, filtered through a short column of celite and the filtrate was mixed with some silica gel to dry load it and flash with the Isolera (5% EtOAc in cyclohexane -> 10% EtOAc in cyclohexane over 10 CV, 100 g SiOH, 254 nm or 280 nm, eluted after 5 CV), giving 1.33 g (65%, 7.8 mmol) of dialdehyde **1.46** as yellow crystals. (This particular reaction was performed by Enrique Blanco).

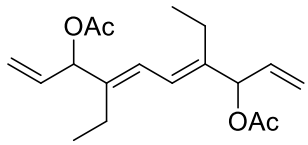
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.22 (s, 1H), 2.53 (q, *J* = 7.6 Hz, 2H), 1.08 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 194.08, 150.14, 139.57, 18.14, 14.03.

Analytical data is in agreement with the previously reported by Breitmaier.[170]



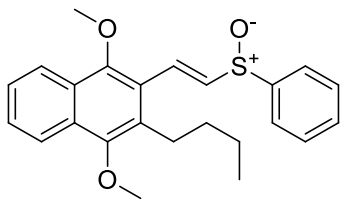
Diallyl alcohol 1.47: A dry round bottom flask under a N_2 atmosphere was charged with 670 mg (4.03 mmol, 1 eq) dialdehyde **1.46** and then dissolved in 20 mL dry THF. The solution was cooled to 0°C before 8.47 mL (8.06 mmol, 2.1 eq) of a 1 M vinyl-MgBr solution in THF was added dropwise. Upon addition, the solution instantly turned darker and a suspension resulted. After 30 min, 25 mL of water was added to the slurry and a colorless solution was obtained, which was extracted three times with 25 mL DCM after a few drops of concentrated aqueous HCl were added to help dissolve the slime and help with the phase separation. The combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Depending on the batch, the product was either pure enough for use without purification or if not it was purified by chromatography with the Isolera (cyclohexane -> 25% EtOAc in cyclohexane over 14 CV, 50 g SiOH, 254 nm or $KMnO_4$, eluted after 12 CV). 482 mg (54%, 2.17 mmol) of diallyl alcohol **1.47** was obtained as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32 (s, 2H), 5.86 (ddd, *J* = 17.0, 10.3, 6.1 Hz, 2H), 5.32 (dt, *J* = 17.2, 1.4 Hz, 2H), 5.18 (dt, *J* = 10.3, 1.3 Hz, 2H), 4.64 (d, *J* = 6.1 Hz, 2H), 2.32 – 2.22 (m, 2H), 2.20 – 2.11 (m, 2H), 1.06 (t, *J* = 7.6 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.20, 139.33, 120.44, 120.43, 115.60, 77.34, 77.32, 21.12, 14.66 (two morel signals than expected are observed due to the mixture of diastereomers). **HRMS** [M+Na^+] calc. for $C_{14}H_{22}NaO_2$: 254.1512, found: 254.1514.



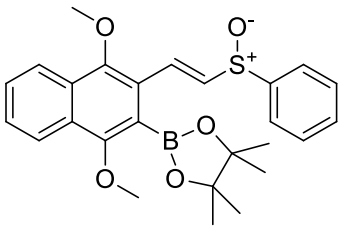
Diallyl acetate 1.49: A dry round bottom flask under a N_2 atmosphere was charged with 139 mg (625 μmol, 1 eq) diallyl alcohol **1.47** as a solution in 6 mL DCM, then with 236 μL (255 mg, 2.5 mmol, 4 eq) Ac_2O, followed by 260 μL (190 mg, 1.88 mmol, 3 eq) NEt_3. At last, 76 mg (625 μmol, 1 eq) DMAP was added and the solution was stirred at room temperature for 1.5 h. Then, 10 mL of saturated, aqueous NH_4Cl solution was added and another 10 mL of DCM. After separation of the fractions, the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 160 mg (84%, 525 μmol) of diallyl alcohol **1.49** as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (s, 2H), 5.85 – 5.74 (m, 2H), 5.70 (d, *J* = 6.1 Hz, 2H), 5.27 (dt, *J* = 17.1, 1.2 Hz, 2H), 5.21 (dt, *J* = 10.3, 1.2 Hz, 2H), 2.26 – 2.13 (m, 4H), 2.08 (s, 6H), 1.04 (t, *J* = 7.6 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.00, 141.92, 141.89, 135.32, 122.36, 122.34, 117.12, 78.38, 78.37, 21.38, 14.29 (two morel signals than expected are observed due to the mixture of diastereomers). **HRMS** [M+Na^+] calc. for $C_{18}H_{26}NaO_4$: 329.1723, found: 329.1724.



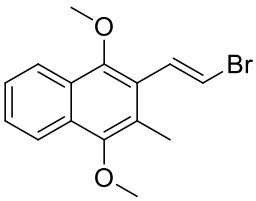
Butyl hydroquinone 1.51: A dry round bottom flask under a N_2 atmosphere was charged with 35 mg (83.9 μmol, 1 eq) hydroquinone **1.40**, which was dissolved in 1 mL dry toluene. Then, 51 μL (58 mg, 101 μmol, 1.2 eq) hexabutyl distannane was added, followed by 4.3 mg (8.39 μmol, 0.1 eq) Pd(P*t*$Bu_3)_2$. The solution was immersed into a preheated oil bath at 70°C and stirred for 19 h overnight. All volatiles were removed and the remains were dissolved in a small amount of DCM to dry load and purify by flash chromatography with the Isolera (10% EtOAc in cyclohexane -> 25% EtOAc in cyclohexane over 14 CV, 25 g SiOH, 254 nm, eluted after 8 CV). 20 mg (38%, 31.8 μmol) of butyl hydroquinone **1.51** were obtained as yellow oil.

R_f = 0.50 (33% EtOAc in cyclohexane), **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 – 8.01 (m, 2H), 7.74 – 7.71 (m, 2H), 7.56 – 7.45 (m, 6H), 7.27 (d, *J* = 15.4 Hz, 1H), 3.90 (s, 3H), 3.64 (s, 3H), 2.94 – 2.86 (m, 2H), 1.56 – 1.50 (m, 2H), 1.39 – 1.33 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (128 MHz HMBC/HMQC, $CDCl_3$) δ 151.81, 150.00, 144.06, 138.74, 131.04 (2C), 129.55, 129.26, 128.76, 127.53, 126.93, 126.05, 124.56, 123.04, 122.98, 122.42, 62.19, 60.84, 33.22, 26.87, 17.29, 13.83. **HRMS** [M+H$^+$] calc. for $C_{24}H_{27}O_3S$: 395.1675, found: 395.1682.



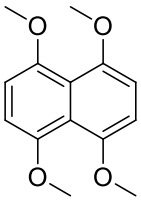
Pinacol boronic acid 1.52: A dry round bottom flask under a N_2 atmosphere was charged with 160 mg (383 μmol, 1 eq) hydroquinone **1.40**, which was dissolved in 10 mL dry dioxane. Then, 111 μL (98 mg, 767 μmol, 2 eq) H-BPin were added, followed by 161 μL (116 mg, 1.15 mmol, 3 eq) dry NEt_3 and 19.6 mg (38.3 μmol, 0.1 eq) $Pd(PtBu_3)_2$. The solution was immersed into a preheated oil bath at 100°C and stirred for 45 min, before it was allowed to cool to room temperature. The mixture was poured into 10 mL water in a separation funnel and another 20 mL Et_2O were added. After separation, the organic fraction was washed with H_2O twice, before it was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was then purified by flash chromatography with the Isolera (15% EtOAc in cyclohexane -> 25% EtOAc in cyclohexane over 14 CV, 25 g SiOH, 254 nm, eluted after 8-10 CV) to give 55 mg (31%, 119 μmol) pinacol boronic acid **1.51** as yellowish solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 – 8.06 (m, 1H), 8.05 – 8.01 (m, 1H), 7.73 – 7.69 (m, 2H), 7.64 (d, *J* = 15.5 Hz, 1H), 7.55 – 7.45 (m, 5H), 7.25 (d, *J* = 15.5 Hz, 1H) 3.97 (s, 3H), 3.74 (s, 3H), 1.43 (s, 6H), 1.42 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.88, 152.13, 144.37, 137.39, 132.46, 131.11, 130.04, 129.51, 128.90, 127.29, 127.13, 125.23, 124.86, 123.25, 122.69, 84.81 (2C), 63.68, 61.59, 25.24, 25.14 (One signal missing due to quadrupole line broadening from boron). **HRMS** [M+H$^+$] calc. for $C_{26}H_{30}BO_5S$: 465.1906, found: 465.1906.

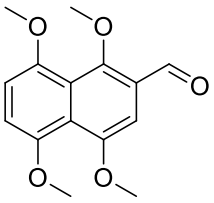


Vinyl bromide 1.58: A dry round bottom flask under a N_2 atmosphere was charged with 55 mg (156 μmol, 1 eq) sulfoxide **1.27k**, which was dissolved in 3 mL dry CCl_4. Then, 28 mg (156 μmol, 1 eq) NBS and 38 mg (156 μmol, 1 eq) BPO were added. The stirring solution was immersed into an oil bath and was heated to 85°C in order to reflux for 5.5 h before it was allowed to cool to room temperature again. After the removal of all volatiles, the residue was dissolved in DMSO and injected into the preparative HPLC (MeCN / 0.1% TFA in H_2O, 2% to 95% over 28 min, 254 nm, t_R = 27 min). After lyophilization, 14 mg (29%, 45.2 μmol) of vinyl bromide **1.58** was isolated as yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.03 (m, 2H), 7.54 – 7.45 (m, 2H), 7.27 (d, *J* = 14.0 Hz, 1H), 7.07 (d, *J* = 14.0 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 2.42 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.53, 150.30, 131.18, 128.46, 127.59, 126.74, 125.99, 125.59, 125.24, 122.85, 122.31, 112.29, 61.58, 61.03, 13.67. **HRMS** [M+Na^+] calc. for $C_{16}H_{15}BrNaO_2$: 329.0148, found: 329.0144.



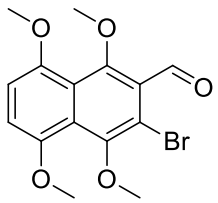
Tetra methoxy naphthalene 1.59 was prepared according to a literature procedure by Choi.[37]



Aldehyde 1.60 (adapted from Sakamoto[38]): A dry round bottom flask under a N_2 atmosphere was charged with 9.13 mL (13.5 g, 106 mmol, 6 eq) $(COCl)_2$ and cooled to roughly 10°C with a water bath containing some ice. Subsequently, 8.18 mL (7.77 g, 106 mmol, 6 eq) DMF was added dropwise to the stirring $(COCl)_2$. The obtained white solid was stirred for 15 min at room temperature before 45 mL dry $CHCl_3$ was added. Then, 4.4 g (17.7 mmol, 1 eq) naphthalene **1.59** as a solution in 25 mL dry $CHCl_3$ was added dropwise at room temperature before the flask was immersed into a preheated oil bath at 60°C and the solution was stirred for 6.5 h. After the solution was allowed to cool to room temperature it was poured into a separation funnel containing 100 mL H_2O and the mixture was extracted 4 times with 100 mL $CHCl_3$. The combined organic fractions were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. After purification by flash chromatography with the Isolera (10% EtOAc in cyclohexane -> 25% EtOAc in cyclohexane over 13 CV, 340 g SiOH, 254 nm, eluted after 10-12 CV) 4.31 g (88%, 15.6 mmol) of aldehyde **1.60** was obtained as yellow solid.

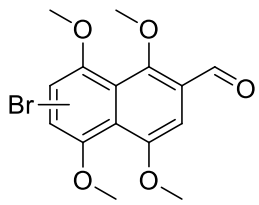
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.56 (s, 1H), 7.20 (s, 1H), 7.04 (d, *J* = 8.7 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 1H), 4.00 (s, 3H), 3.98 (s, 3H), 3.92 (s, 3H), 3.91 (s, 3H).

Analytical data is in agreement with the previously reported by Sakamoto.[38]



Bromide 1.61 (Adapted from Trofimov[171]): A dry round bottom flask under a N_2 atmosphere was charged with 207 μL (163 mg, 1.59 mmol, 1.1 eq) *N*,*N*,*N*'-trimethylethylenediamine, which was dissolved in 20 mL dry toluene. The solution was cooled to 0°C and 981 μL (1.52 mmol, 1.05 eq) *n*-BuLi as 1.55 M solution in hexane was added dropwise. After stirring for 15 min at 0°C the solution was allowed to warm to room temperature and 400 mg (1.45 mmol, 1 eq) aldehyde **1.60** was added, which stirred for 15 min at room temperature. After cooling again to 0°C, 2.34 mL (3.62 mmol, 2.5 eq) *n*-BuLi as 1.55 M solution in hexane was added dropwise over 45 min by syringe pump and the solution was allowed to stir at 0°C for another 30 min before it was allowed to warm up to room temperature. After stirring for 4 h at room temperature, it was cooled to -78°C and 2.4 g (7.24 mmol, 5 eq) CBr_4 was added in one scoop and the solution stirred for another 15 min at -78°C before it was allowed to warm to room temperature. The slurry stirred at room temperature overnight and was then poured into a separation funnel containing 20 mL water. After separation, the aqueous layer was extracted 3 times with Et_2O, the combined organic fractions dried over Na_2SO_4, filtered, and concentrated under reduced pressure. After purification by flash chromatography with the Isolera (5% EtOAc in cyclohexane -> 20% EtOAc in cyclohexane over 15 CV, 100 g SiOH, 254 nm, eluted after 13-14 CV) 88 mg (17%, 247 μmol) of bromide **1.61** was obtained as yellow solid.

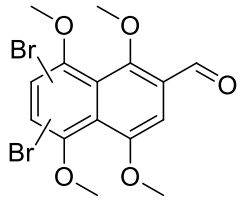
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.48 (s, 1H), 7.03 (d, *J* = 8.7 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.95, 157.57, 151.71, 150.56, 149.80, 126.49, 125.50, 121.79, 113.59, 111.99, 108.55, 65.21, 61.89, 57.76, 57.10. **HRMS** [M+Na^+] calc. for $C_{15}H_{15}BrNaO_5$: 376.9995, found: 376.9997.



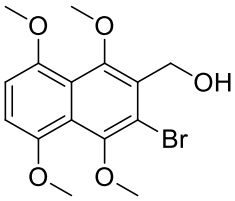
Byproduct **bromide 1.62** was isolated after 10-11 CV:

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.52 (s, 1H), 7.24 (s, 1H), 7.12 (s, 1H), 4.01 (s, 3H), 4.00 (s, 3H), 3.90 (s, 3H), 3.82 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 189.93, 157.25, 153.64, 152.37, 147.50, 126.83, 126.31, 121.86, 119.74, 112.42, 102.68, 65.73, 62.08, 56.90, 56.70. **HRMS** [M+Na^+] calc. for $C_{15}H_{15}BrNaO_5$: 376.9995, found: 376.9997.

Byproduct **dibromide 1.63** was isolated after 6-7 CV:

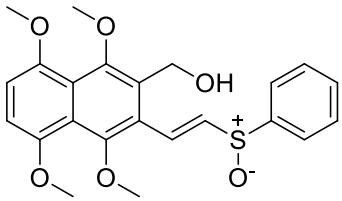


^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 1H), 7.10 (s, 1H), 3.99 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.48, 157.83, 154.02, 149.13, 145.71, 128.10, 126.57, 121.07, 120.20, 115.35, 112.25, 65.33, 62.33, 62.20, 56.96. **HRMS** [M+Na^+] calc. for $C_{15}H_{14}BrNaO_5$: 454.9100, found: 454.9100.



Alcohol 1.64: A dry round bottom flask under a N_2 atmosphere was charged with 59 mg (166 μmol, 1 eq) bromide **1.61**, which was dissolved in 2 mL dry THF with the help of sonication and cooled to 0°C. Then, 25 mg (664 μmol, 4 eq) LAH was added in two portions to the stirred solution and the mixture was kept at 0°C for another 10 min. After allowing the mixture to warm to room temperature it was stirred for another 2 h at room temperature, before 2 mL 1M aqueous HCl solution was added dropwise. The obtained biphasic slurry was extracted 3 times with $CHCl_3$ and the combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure, which gave 52 mg (89%, 148 μmol) **1.64** as pale yellow resin, which was used without further purification in the next step

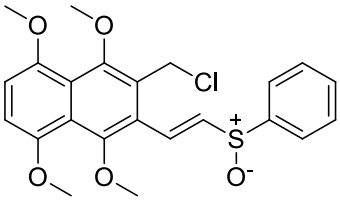
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, *J* = 8.7 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 5.03 (s, 2H), 3.95 (s, 3H), 3.94 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.07, 150.61, 149.92, 149.91, 131.16, 123.42, 122.05, 118.77, 109.04, 107.96, 63.93, 61.86, 60.76, 57.56, 57.13. **HRMS** [M+Na^+] calc. for $C_{15}H_{17}BrNaO_5$: 379.0152, found: 379.0151.



Sulfoxide 1.65: A dry round bottom flask under a N_2 atmosphere was charged with 140 mg (392 μmol, 1 eq) alcohol **1.64**, which was dissolved in 5 ml dry dioxane. Then, 52 μL (60 mg, 392 μmol, 1 eq) phenyl vinylsulfoxide, 109 μL (79 mg, 784 μmol, 2 eq) NEt_3 and 40 mg (78.4 μmol, 0.2 eq) $Pd(PtBu_3)_2$ were added in the given sequence. The solution was immersed into a preheated oil bath at 80°C and stirred for 1h before the slurry was allowed to cool to room temperature. All solvents were removed and the remains were dry loaded to purify by manual flash chromatography (80% EtOAc in cyclohexane, 15 g SiOH, 254 nm and 365 nm, eluted in F25-71 of 6 mL, strong smearing. For optimization, reverse phase chromatography is suggested). After

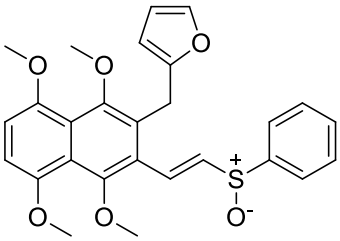
concentration of the yellow fractions, 91 mg (54%, 212 μmol) of **1.65** was obtained as foamy yellow solid.

R_f = 0.30 (80% EtOAc in cyclohexane), **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 – 7.68 (m, 3H), 7.53 – 7.42 (m, 3H), 7.27 (d, *J* = 15.6 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 1H), 4.87 (d, *J* = 11.5 Hz, 1H), 4.83 (d, *J* = 11.5 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.80 (s, 3H), 3.58 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.00, 151.82, 150.71, 150.24, 144.17, 139.57, 131.07, 129.64, 129.47, 129.38, 126.15, 124.73, 122.69, 122.66, 108.39, 107.84, 63.60, 61.91, 57.22, 57.08, 56.98. **HRMS** [M+Na^+] calc. for $C_{23}H_{24}NaO_6S$: 451.1186, found: 451.1184.



Chloride 1.66: A dry round bottom flask under a N_2 atmosphere was charged with 11 mg (25.7 μmol, 1 eq) alcohol **1.65** as a solution in benzene. After the removal of all volatiles under reduced pressure, 0.5 mL DCM was added. After cooling the solution to 0°C, first 33 μL (257 μmol, 10 eq) DBU, then 20 μL (257 μmol, 10 eq) MsCl were added dropwise to the stirring solution. The solution stirred for 10 min at 0°C before it was allowed to warm to room temperature and stirred for another 2 h. Then, all volatiles were removed under reduced pressure and the residue was purified by manual flash chromatography (33% EtOAc in cyclohexane, 15 g SiOH, 254 nm, eluted in F18-28 of 5 mL). After concentration of the yellow fractions, 6 mg (52%, 13.4 μmol) of chloride **1.66** was obtained as yellow oil.

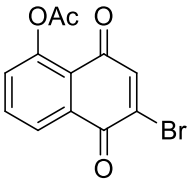
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.71 (m, 2H), 7.64 (d, *J* = 15.5 Hz, 1H), 7.56 – 7.45 (m, 3H), 7.32 (d, *J* = 15.5 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 1H), 4.90 (d, *J* = 11.0 Hz, 1H), 4.86 (d, *J* = 11.0 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 3.88 (s, 3H), 3.58 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.10, 152.04, 150.70, 150.44, 144.08, 140.15, 131.21, 129.56, 128.22, 126.98, 125.38, 124.77, 123.17, 122.57, 108.56, 108.43, 63.62, 61.87, 57.10, 57.04, 38.82. **HRMS** [M+Na^+] calc. for $C_{23}H_{23}ClNaO_5S$: 469.0847, found: 469.0847.



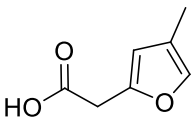
Furan 1.67: A dry round bottom flask under a N_2 atmosphere was charged with 6 mg (13.4 μmol, 1 eq) chloride **1.66** as a solution in benzene. After the removal of all volatiles under reduced pressure, 0.5 mL dry dioxane was added, followed by 8 μL (9.6 mg, 26.8 μmol, 2 eq) 2-furyl tributylstannane and 2 mg (4.02 μmol, 0.3 eq) $Pd(PtBu_3)_2$. The solution was immersed into a preheated oil bath at 80°C and stirred for 1.5h before it was allowed to

cool to room temperature and all volatiles were removed under reduced pressure. The residue was purified by manual flash chromatography (25% EtOAc in cyclohexane 3 CV, then 33% EtOAc in cyclohexane 4 CV, 5 g SiOH, 254 nm, eluted in F24-34 of 5 mL). After concentration of the yellow fractions, 2 mg (31%, 4.15 μmol) of furan **1.67** was obtained as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.57 (m, 2H), 7.51 – 7.44 (m, 4H), 7.28 – 7.27 (m, 1H), 7.12 (d, *J* = 15.5 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 1H), 6.23 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.88 – 5.85 (m, 1H), 4.29 (d, *J* = 16.0 Hz, 1H), 4.23 (d, *J* = 16.1 Hz, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.71 (s, 3H), 3.57 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.08, 152.05, 151.03, 150.81, 150.11, 144.11, 141.28, 139.20, 131.03, 129.57, 129.43, 127.64, 126.04, 124.82, 122.88, 122.17, 110.45, 108.49, 107.16, 106.74, 62.91, 61.71, 57.23, 56.91, 26.13. **HRMS** [M+H$^+$] calc. for $C_{27}H_{27}O_6S$: 479.1523, found: 479.1523.

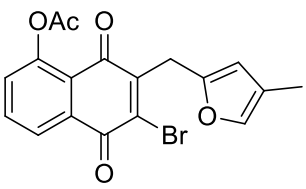


Juglone 1.69 was prepared according to a literature procedure by Ishikawa.[42]



Furan 1.70: A round bottom flask under a N_2 atmosphere was charged with 1 g (6.49 mmo, 1 eq) furan **1.74** (*vide infra*), which was dissolved in 25 mL THF. Then, 25 mL H_2O containing 4.16 g LiOH x H_2O was added. The solution stirred at room temperature for 2 h, before the alkaline reaction was acidified carefully with 9 mL concentrated aqueous HCl. The biphasic mixture was extracted twice with 50 mL Et_2O, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by manual flash chromatography (25% EtOAc in cyclohexane plus 0.25% AcOH, 50 g SiOH, 254 nm or $KMnO_4$). After concentration of the colorless fractions, 750 mg (83%, 5.39 mmol) of furan **1.70** was obtained as colorless solid/crystals.

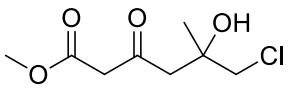
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.13 (m, 1H), 6.12 (s, 1H), 3.68 (s, 2H), 2.00 (d, *J* = 1.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.51, 146.88, 139.11, 121.10, 111.35, 33.96, 9.88. **HRMS** [M+Na$^+$] calc. for $C_7H_8NaO_3$: 163.0366, found: 163.0366.



Juglone 1.71: A round bottom flask under a N_2 atmosphere was charged with 40 mg (136 μmol, 1 eq) juglone **1.69** and 25 mg (176 μmol, 1.3 eq) furan **1.70**, which were subsequently dissolved in 1 mL degassed acetone. Then, 7 mg (40.7 μmol, 0.3 eq) $AgNO_3$ was added and the slurry was immersed into a preheated oil bath at 60°C. A solution of 141 mg (678 μmol, 5 eq) $(NH_4)_2S_2O_8$ in

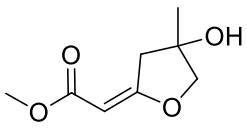
1 mL degassed H_2O was added fast. After exactly 5 minutes at 60°C, the heating was removed and 25 mL $CHCl_3$ was added, followed by 25 mL H_2O. The organic phase was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The remains were dry loaded and purified by flash chromatography with the Isolera (10% EtOAc in cyclohexane -> 35% EtOAc in cyclohexane over 14 CV, 25 g SiOH, 254 nm, eluted after 5 CV), giving 22 mg (42%, 57.1 μmol) of juglone **1.71** as brown solid. On a larger scale (up to 1.2 g of **1.69**) yields in the range of 15% were obtained. No full conversion was obtained and **1.69** coeluted with **1.71** on normal phase silica gel. A second purification by preparative HPLC (MeCN / H_2O, 10 to 80% over 20 min, 254 nm, t_R = 19 min) after chromatography with the Isolera allowed the isolation of clean **1.71**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.74 (t, *J* = 7.9 Hz, 1H), 7.40 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.06 – 7.05 (m, 1H), 5.99 (s, 1H), 4.14 (d, *J* = 0.5 Hz, 2H), 2.46 (s, 3H), 1.95 (d, *J* = 1.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.70, 177.45, 169.46, 150.12, 149.10, 148.04, 138.96, 138.51, 134.90, 132.90, 130.33, 126.22, 123.06, 121.00, 110.36, 30.27, 21.26, 9.89. **HRMS** [M+Na$^+$] calc. for $C_{18}H_{13}BrNaO_5$: 410.9839, found: 410.9837.



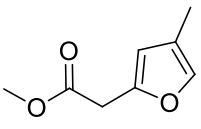
Acetonate 1.72: Followed the general procedure by Weiler[41]. Accordingly, a dry round bottom flask under a N_2 atmosphere was charged with 3.80 g (95.0 mmol, 2.2 eq, 60% pure) NaH in mineral oil and 240 mL dry THF was added. The slurry was cooled to 0°C and 10 g (86.5 mmol, 2 eq) methyl acetoacetate was added dropwise while stirring and the slurry was kept for another 10 min at 0°C. Afterwards, 56.7 mL (90.7 mmol, 2.1 eq) *n*-BuLi 1.6 M in hexane was added dropwise. The obtained yellow mixture was stirred for 10 min at 0°C before 3.56 mL (4g, 43.2 mmol, 1eq) chloro acetone *(hazardous, lacrimation agent*) was added with a syringe in one portion. After another 10 min at 0°C the reaction was quenched by addition of 45 mL concentrated aqueous HCl and the mixture was poured into a separation funnel containing 200 mL Et_2O. The layers were separated and the aqueous phase was extracted two more times with 100 mL Et_2O. Crude ^{1}H NMR analysis suggested a mixture of methyl acetoacetate and desired acetonate **1.72**, which was used in the next step without further purification

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, *J* = 1.4 Hz, 3H), 3.59 (d, *J* = 11.0 Hz, 1H), 3.54 – 3.50 (m, 4H), 3.04 (d, *J* = 17.3 Hz, 1H), 2.76 (d, *J* = 17.3 Hz, 1H), 1.34 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 203.65, 167.17, 71.94, 52.68, 51.94, 50.40, 49.40, 25.40.



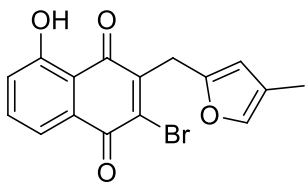
Tetrahydrofuran 1.73: Assuming no loss of material, the crude product (*vide supra*) **1.72** (43.2 mmol, 1 eq) was dissolved in a round bottom flask in 240 mL DCM and then 11.2 mL (13.2 g, 86.5 mmol, 2 eq) DBU was added dropwise. The solution was stirred at room temperature for 30 min, before it was transferred into a separation funnel and washed once with 240 mL saturated aqueous NH_4Cl solution to remove the DBU. Subsequently, the organic layer was dried over $MgSO_4$, filtered and concentrated to ca. 250 mL, giving crude **1.73** with impurities, which was used in the next step without further purification

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 – 5.37 (m, 1H), 4.18 (dd, *J* = 9.5, 1.1 Hz, 1H), 3.99 (d, *J* = 9.5 Hz, 1H), 3.66 (s, 3H), 3.47 (d, *J* = 18.3 Hz, 1H), 2.92 (dd, *J* = 18.3, 2.2 Hz, 1H), 1.50 (s, 3H).



Furan 1.74: Assuming no loss of material, the crude product (*vide supra*) **1.73** (43.2 mmol, 1 eq) as solution in DCM was stirred at 0°C under a N_2 atmosphere, while 8.03 mL (12.3 g, 108 mmol, 2.5 eq) TFA was added dropwise. Cooling was removed and the solution stirred 1 h at room temperature, before saturated aqueous $NaHCO_3$ was added until gas formation ceased. The layers were separated, the organic fraction dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a brown liquid. The crude material was purified by manual flash chromatography (11% EtOAc in cyclohexane (1:8), 180 g SiOH, $KMnO_4$, first spot on TLC, eluted just after the first yellow band) and gave 1.0 g (15% over 3 steps, 6.48 mmol) of furan **1.74** as yellow oil.

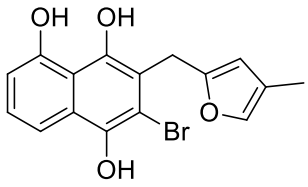
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.11 (m, 1H), 6.09 (s, 1H), 3.72 (s, 6H), 3.64 (s, 2H), 2.00 (d, *J* = 1.1 Hz, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.14, 147.66, 138.88, 121.02, 110.95, 52.40, 34.18, 9.89. **HRMS** [M+Na^+] calc. for $C_8H_{10}NaO_3$: 177.0522, found: 177.0521.



Juglone 1.75: A dry round bottom flask under a N_2 atmosphere was charged with 200 mg (514 μmol, 1 eq) juglone **1.71**, which was dissolved in 8 mL THF and 4 mL H_2O. Then, 86.3 mg (2.06 mmol, 4 eq) LiOH x H_2O was added in one scoop and the solution turned violet instantly. After 10 min stirring at room temperature, 2 mL 1N aqueous HCl was added dropwise and the mixture was transferred into a separation funnel. After separation, the aqueous phase was extracted twice with 10 mL Et_2O, before the combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by manual flash chromatography (10%

EtOAc in cyclohexane, 30 g SiOH, 254 nm or $KMnO_4$, first yellow band) and gave 128 mg (72%, 370 μmol) juglone **1.75** as orange solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.90 (s, 1H, Ar-OH), 7.72 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.63 (dd, *J* = 8.5 Hz, 7.5, 1H), 7.29 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.09 – 7.06 (m, 1H), 6.06 (s, 1H), 4.19 (s, 2H), 1.97 (d, *J* = 1.1 Hz, 3H). This is preliminary data which was not reproduced. Thus, unfortunately only limited analytical data can be given.

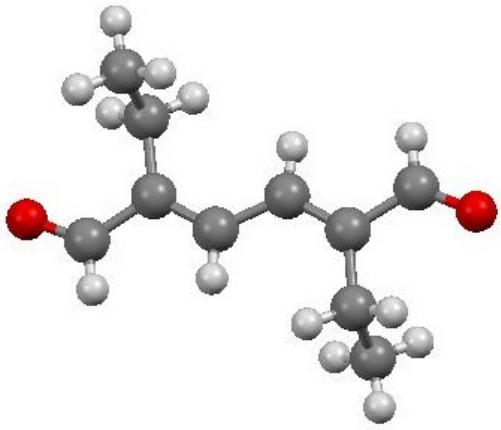


Hydroquinone 1.76: A round bottom flask was charged with 4.5 mg (13.0 μmol, 1 eq) juglone **1.75**, which was dissolved in 300 μL Et_2O, 300 μL H_2O and 30 μL EtOAc. Then, 5.3 mg (25.9 μmol, 2 eq, 85% purity, technical grade) sodium dithionite ($Na_2S_2O_4$) was added in one portion and the biphasic mixture stirred at room temperature for 30 min before the phases were separated. The organic phase was concentrated under reduced pressure. ^{1}H NMR analysis of the crude product revealed 65% conversion to desired hydroquinone **1.76** together with starting material **1.75** and without any byproducts.

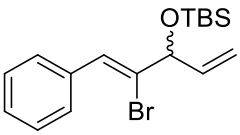
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (s, 1H, Ar-OH), 7.85 (s, 1H, Ar-OH), 7.70 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.32 (dd, *J* = 8.4, 7.7 Hz, 1H), 7.10 – 7.09 (m, 1H), 6.87 (dd, *J* = 7.6, 1.0 Hz, 1H), 6.00 (s, 1H, Ar-OH), 5.75 (s, 1H), 4.25 (d, *J* = 0.5 Hz, 2H), 1.96 (d, *J* = 1.2 Hz, 3H). This is preliminary data which was not reproduced. Thus, unfortunately only limited analytical data can be given.

5.2.4 Crystallographic Data

Crystal data for **1.46**: formula $C_{10}H_{14}O_2$, M = 166.22, F(000) = 720, colorless prism, size 0.040 · 0.110 · 0.190 mm^3, orthorhombic, space group P 2_1 2_1 2_1, Z = 8, a = 9.7609(4) Å, b = 12.6478(3) Å, c = 14.9344(5) Å, α = 90°, β = 90°, γ = 90°, V = 1843.71(11) $Å^3$, $D_{calc.}$ = 1.198 Mg · m^{-3}. The crystal was measured on a Bruker Kappa Apex2 diffractometer at 123K using graphite-monochromated Mo K_α-radiation with λ = 0.71073 Å, Θ_{max} = 27.541°. Minimal/maximal transmission 0.99/1.00, μ = 0.082 mm^{-1}. The Apex2 suite has been used for datacollection and integration. From a total of 15165 reflections, 2419 were independent (merging r = 0.057). From these, 1975 were considered as observed (I>2.0σ(I)) and were used to refine 217 parameters. The structure was solved by other methods using the program Superflip. Least-squares refinement against F was carried out on all non-hydrogen atoms using the program CRYSTALS. R = 0.0423 (observed data), wR = 0.0743 (all data), GOF = 1.1003. Minimal/maximal residual electron density = -0.19/0.22 e $Å^{-3}$. Chebychev polynomial weights were used to complete the refinement.

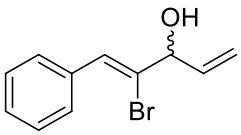


5.3 Syntheses towards LNA



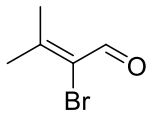
TBS-protected alcohol *rac* 2.18: In a dry round bottom flask 670 mg (2.80 mmol, 1 eq) of alcohol **2.23** was dissolved in 10 mL of dry DMF and 634 mg (4.21 mmol, 1.5 eq) TBS-Cl was added. Then, the stirring reaction was immersed into a room temperature water bath to control the heat generation of the subsequent addition of 477 mg (7.01 mmol, 2.5 eq) imidazole in one scoop. The solution was allowed to stir overnight before it was poured into a separation funnel containing 20 mL of water and was extracted 3 times with 30 mL pentane. The combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography with Isolera (0% EtOAc in cyclohexane -> 3% EtOAc in cyclohexane, 50g SiOH, 254 nm, elutes after 3-6 CV) and yielded 851 mg (2.41 mmol, 86%) of ***rac* 2.18** as pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.60 (m, 2H), 7.39 – 7.34 (m, 2H), 7.33 – 7.27 (m, 1H), 7.18 (s, 1H), 5.94 (ddd, *J* = 17.0, 10.2, 5.5 Hz, 1H), 5.42 (dt, *J* = 17.0, 1.5 Hz, 1H), 5.25 (dt, *J* = 10.2, 1.4 Hz, 1H), 4.81 – 4.78 m, 1H), 0.96 (s, 9H), 0.14 (s, 3H), 0.14 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.20, 135.47, 129.09, 128.38, 128.12, 127.94, 126.84, 116.17, 78.86, 25.82, 18.38, -4.77, -4.79. HRMS: did not ionize.



Alcohol 2.23: In a dry round bottom flask under a N_2 atmosphere 13.5 mL (9.48 mmol, 2 eq) 0.7 M vinyl magnesium bromide in THF was added to a stirring solution of 1 g (4.74 mmol, 1 eq) 2-bromo cinnamaldehyde in 50 mL THF at room temperature. The solution stirred at room temperature for 2 h before 1.8 mL (14.2 mmol, 3 eq) TMS-Cl was added and the solution stirred for another hour at room temperature (remark: a TMS protection was attempted, which failed, but this procedure gave the highest yields) before it was transferred into a separation funnel and quenched with an equal amount of H_2O. The mixture was subsequently diluted with Et_2O, the organic fraction collected and the aqueous fraction was once extracted with diethyl Et_2O. After combining both ether fractions, they were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography with Isolera (10% EtOAc in cyclohexane -> 17% EtOAc in cyclohexane, 50 g SiOH, 254 nm, eluted after 3-5 CV) yielded 948 mg (84%, 3.93 mmol) of alcohol **2.23** as yellow oil.

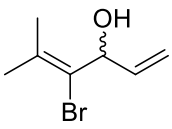
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.60 (m, 2H), 7.39 – 7.35 (m, 2H), 7.34 – 7.30 (m, 1H), 7.14 (s, 1H), 6.01 (ddd, *J* = 17.2, 10.4, 5.4 Hz, 1H), 5.48 (dt, *J* = 17.2, 1.3 Hz, 1H), 5.35 (dt, *J* = 10.4, 1.3 Hz, 1H), 4.85 (t, *J* = 5.4 Hz, 1H), 2.26 (d, *J* = 6.1 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.51, 135.07, 129.26, 128.74, 128.43, 128.33, 128.20, 117.55, 78.18.



Acrolein 2.26: To a solution of 2.3 mL (2 g, 0.024 mol, 1 eq) 3,3-dimethyl acrolein in 25 mL DCM was added 1.28 mL (3.99 g, 0.025 mol, 1.05 eq) bromine dropwise at 0°C and then allowed to stir for another 10 min at 0°C, before 30 mL saturated aqueous $Na_2S_2O_3$ was added. After stirring for 10 min at room temperature, the product was extracted twice with 40 mL of DCM and the combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure, to give a crude dibromide intermediate. It was dissolved in 100 mL of DCM and cooled to 0°C while stirring, before 3.32 mL (2.4 g, 0.024 mol, 1 eq) NEt_3 was added dropwise. The slurry was allowed to stir for 1 h at 0°C before it was transferred into a separation funnel and washed twice with saturated aqueous NH_4Cl. The organic fraction was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 3.84 g (99%, 0.024 mol) of **2.26** as a colorless oil in good purity. It was used for the synthesis of alcohol **2.27** without further purification. It should be stored at -20°C.

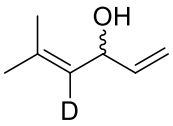
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 2.35 (s, 3H), 2.21 (s, 3H).

Analytical data is in agreement with the previously reported by Massefski.[172]



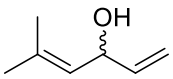
Allyl alcohol 2.27: In a dry round bottom flask 9.64 mL (6.75 mmol, 1.1 eq) 0.7 M vinyl magnesium bromide in THF was added to a stirring solution of 1 g (6.14 mmol, 1 eq) acrolein **2.26** in 20 mL THF at room temperature. The solution stirred at room temperature for 2 h before 2 mL of saturated aqueous 1M HCl was slowly added. The mixture was subsequently transferred into separation funnel and 50 mL of water was added, then 50 mL Et_2O. After separation of the aqueous phase, the organic phase was treated with an equal amount of brine, separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography with Isolera (5% EtOAc in cyclohexane -> 15% EtOAc in cyclohexane, 50 g SiOH, 254 nm better $KMnO_4$, elutes after 4-6 CV, broad peak) and yielded 556 mg (47%, 2.89 mmol) of **2.27** as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddd, *J* = 17.2, 10.4, 4.8 Hz, 1H), 5.33 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.23 (dt, *J* = 10.4, 1.4 Hz, 1H), 5.10 – 5.05 (m, 1H), 1.92 (s, 3H), 1.89 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.26, 133.55, 124.31, 115.90, 71.35, 25.67, 21.02. HRMS: did not ionize.



Deuterated allyl alcohol 2.29: A dry round bottom flask under a N_2 atmosphere was charged with 55 mg (0.288 mmol, 1 eq) of alcohol **2.27** as a solution in benzene and all volatiles were subsequently removed under reduced pressure. The residue was dissolved in 1 ml of dry THF and cooled to -78°C before 0.2 mL (0.317 mmol, 1.1 eq) MeLi 1.6 M in Et_2O was added dropwise. After letting the solution to stir for 10 min at -78°C, 0.4 mL (0.633 mmol, 2.2 eq) *t*-BuLi 1.6 M in pentane was added dropwise. The yellow solution was again stirred for 10 min at -78°C before the reaction was quenched with 0.2 mL (10 mmol, 35 eq) of D_2O at -78°C. After 10 min stirring, the slurry was allowed to warm to room temperature. After concentration under reduced pressure, clean **2.29** was obtained. No purification was performed, thus no accurate yield can be given.

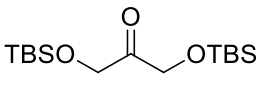
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddd, *J* = 17.2, 10.3, 5.8 Hz, 1H), 5.22 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.08 (dt, *J* = 10.3, 1.4 Hz, 1H), 4.85 (d, *J* = 5.6 Hz, 1H), 1.74 (s, 3H), 1.71 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.17, 135.80, 125.72 (t, *J* = 23.5 Hz, C-D), 114.21, 70.06, 25.86, 18.31.



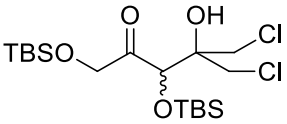
Diallylalcohol 2.30: A dry round bottom flask under a N_2 atmosphere was charged with 62 mg (0.324 mmol, 1 eq) **2.27** as a solution in benzene and all volatiles were subsequently removed under reduced pressure. The residue was dissolved in 1 mL of dry THF and cooled to -78°C before 0.22 mL (0.357 mmol, 1.1 eq) MeLi 1.6 M in Et_2O was added dropwise. After letting the solution stir for 10 min at -78°C, 0.45 mL (0.714 mmol, 2.2 eq) *t*-BuLi 1.6 M in pentane was added dropwise. The yellow solution was again stirred for 10 min at -78°C before 41 mg (0.324 mmol, 1 eq) 1,3-dichloroacetone was added as a solution in 0.5 mL THF. The solution was stirred at -78°C for another 10 min before it was allowed to warm to room temperature and 65 μL (3.24 mmol, 10 eq) D_2O was added. After concentration of the sample under reduced pressure ca 80% pure **2.30** was obtained.

^{1}H NMR (250 MHz, $CDCl_3$) δ 5.89 (ddd, *J* = 17.2, 10.3, 5.8 Hz, 1H), 5.28 – 5.16 (m, 2H), 5.09 (dt, *J* = 10.3, 1.4 Hz, 1H), 4.90 – 4.81 (m, 1H), 1.75 (d, *J* = 1.3 Hz, 3H), 1.72 (d, *J* = 1.3 Hz, 3H).

Analytical data is in agreement with the previously reported by Lautens.[173]

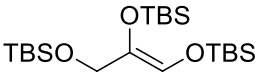


Ketone 2.32: Reproduced according to Tamm.[73] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.41 (s, 4H), 0.92 (s, 18 H), 0.09 (s, 12H).

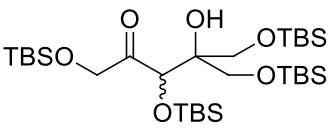


Dichloride 2.33: LDA was prepared in a dry round bottom flask according to the procedure in 5.1.2 [3.9 mL (27.7 mmol, 1.2 eq) DIPA, 17.33 mL (27.7 mmol, 1.2 eq) *n*-BuLi 1.6 M in hexane] in 50 mL of dry THF and cooled to -78°C. Then, 8 mL (7.36 g, 23.1 mmol, 1 eq) **2.32** dissolved in 60 mL of dry THF was added dropwise over 2 h by syringe pump. Upon completion of the addition, the solution was stirred for 15 min at -78°C and then 2.93 g (23.1 mmol, 1 eq) 1,3-dichloroacetone was added as a solution in 40 mL dry THF by syringe pump. Upon completion of the second addition, the solution was stirred for 30 min at -78°C before it was allowed to warm to > 0°C and was then poured into a separation funnel containing 200 mL of water. The aqueous phase was extracted three times with 150 mL Et_2O before the combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by manual flash chromatography (360 g SiOH, 2% EtOAc in cyclohexane, KMnO4, eluted in fractions 29-43 of 75 mL) giving 3.69 g (36%, 8.32 mmol) of **2.33** as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92 (s, 1H), 4.41 (s, 2H), 3.91 (d, *J* = 11.6 Hz, 1H), 3.75 (d, *J* = 11.9 Hz, 1H), 3.71 (d, *J* = 11.9 Hz, 1H), 3.64 (d, *J* = 11.6 Hz, 1H), 3.44 (s, 1H) 0.93 (s, 9H), 0.93 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.05 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.55, 75.83, 74.25, 69.67, 47.34, 46.30, 25.94, 25.78, 18.53, 18.15, -4.65, -5.03, -5.29, -5.30. **HRMS** [M+Na^+] calc. for $C_{18}H_{38}Cl_2NaO_4Si_2$: 467.1578, found: 467.1578.

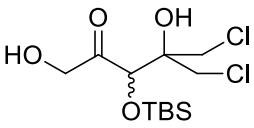


In fractions 23-25, 820 mg of **silyl enol ether 2.33a** was obtained. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.84 (s, 1H), 3.92 (s, 2H), 0.93 (s, 9H), 0.93 (s, 9H), 0.90 (s, 9H), 0.15 (s, 6H), 0.14 (s, 6H), 0.06 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.37, 124.07, 63.44, 26.11, 26.01, 26.00, 18.65, 18.55, 18.46, -4.15, -5.02, -5.11. **HRMS** [M+Na^+] calc. for $C_{21}H_{48}NaO_3Si_3$: 455.2803, found: 455.2808.



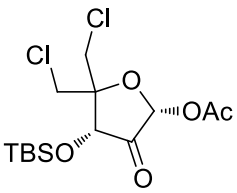
If ketone **2.32** was added too quickly, **homo coupled alcohol 2.39** formed exclusively. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.61 (d, *J* = 18.5 Hz, 1H), 4.55 (d, *J* = 18.5 Hz, 1H), 4.31 (s, 1H), 3.65 (d, *J* = 9.9 Hz, 1H), 3.60 (d, *J* = 7.6 Hz, 1H), 3.60 (d, *J* = 12.3 Hz, 1H), 3.48 (d, *J* = 10.0 Hz, 1H), 2.84 (s, 1H), 0.93 (s, 9H), 0.91 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 6H), 0.06 (s, 3H), 0.06 (s, 3H), 0.05 (s, 6H), 0.04 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.10, 76.67, 76.60, 68.80, 62.27, 25.94, 25.93, 25.91, 25.76, 18.54, 18.32, 18.28, 18.12, -4.92, -5.07, -5.23, -5.30, -5.40 (2C), -5.44, -5.49. One signal missing, probably underneath CDCl3 signal. **HRMS** [M+Na$^+$] calc. for $C_{30}H_{68}NaO_6Si_4$: 659.3985, found: 659.3988.



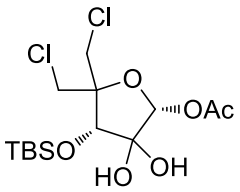
Diol 2.34: A roundbottom flask was charged with 3.69 g (8.27 mmol, 1 eq) dichloride **2.33** and subsequently dissolved in 20 mL THF and 20 mL H_2O. Then, 60 mL AcOH (~140 eq) were added carefully and the reaction was immersed into a heating bath. The solution stirred at 45°C for 3.5 h before it was allowed to cool to room temperature and transferred into a separation funnel. After dilution with 250 mL Et_2O, three washes with 300 mL saturated aqueous $NaHCO_3$ each (slow addition, gas formation!), were done. The organic fraction was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by manual flash chromatography (200 g SiOH, 20% EtOAc in cyclohexane, $KMnO_4$, eluted in fractions 13-22 of 40 mL) giving 2.74 g (74%, 6.12 mmol) of **2.34** as colorless oil.

R_f = 0.25 (20% EtOAc in cyclohexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.55 (dd, *J* = 20.0, 5.4 Hz, 1H), 4.52 (s, 1H), 4.48 (dd, *J* = 20.0, 5.4 Hz, 1H), 3.79 (d, *J* = 11.7 Hz, 2H), 3.74 (d, *J* = 11.6 Hz, 1H), 3.58 (d, *J* = 11.8 Hz, 1H), 2.96 (t, *J* = 5.1 Hz, 1H), 2.87 (s, 1H), 0.95 (s, 9H), 0.14 (s, 6H), 0.07 (s, 6H). **^{13}C NMR** (101 MHz, CDCl3) δ 211.22, 76.62, 76.34, 68.29, 45.97, 45.51, 25.79, 18.17, -4.75, -4.93. **HRMS** [M+Na$^+$] calc. for $C_{12}H_{24}Cl_2NaO_4Si$: 353.0713, found: 353.0717.



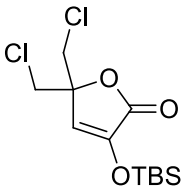
Ketone *rac* 2.35 and corresponding **hydrate *rac* 2.43**: 261 mg (713 μmol, 1 eq) of the crude lactol ***rac* 2.34** (*vide supra*) were dissolved in 7.5 mL THF in a dry round bottom flask under a N_2 atmosphere. Then 7.5 mL (78 mmol, 110 eq) Ac_2O was added before 83 μL (713 μmol, 1 eq) 2,6-Lutidine was added dropwise over ca 3 minutes. The solution was allowed to stir at room temperature for 1.5 h before it was transferred into a bigger flask and diluted with 60 mL toluene. The resulting mixture was concentrated under reduced pressure and the procedure with toluene was repeated two more times. The resulting yellow liquid was then dissolved in 4 mL of MeCN and 1.6 mL 0.1% TFA in H_2O buffer. After stirring for 10 min the solution was divided in two batches and subjected to preparative HPLC (MeCN / 0.1% TFA in H_2O, 20% - 90% over 20 min, t_R = 17.5 min broad peak, 194 nm). After lyophilization 73 mg (28% over two steps, 192 μmol) of hydrate ***rac* 2.43** was obtained as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (s, 1H), 4.36 (s, 1H), 4.06 (s, 1H), 3.98 (d, *J* = 11.3 Hz, 1H), 3.84 (d, *J* = 12.2 Hz, 1H), 3.73 (d, *J* = 12.2 Hz, 1H), 3.63 (d, *J* = 11.2 Hz, 1H), 3.07 (s, 1H), 2.14 (s, 3H), 0.95 (s, 9H), 0.23 (s, 3H), 0.22 (s, 3H). **13C NMR** (101 MHz, CDCl3) δ 170.55, 100.28, 98.09, 84.69, 78.40, 46.30, 45.39, 25.93, 21.41, 18.28, -4.13, -4.88. **LRMS** [M+Na^+] calc. for $C_{14}H_{26}Cl_2NaO_6Si$: 411.1 found: 411.2.



If ***rac* 2.43** was allowed to stand over prolonged time in benzene or if it was co-evaporated multiple times with benzene, the corresponding ketone ***rac* 2.35** was obtained as colorless oil.

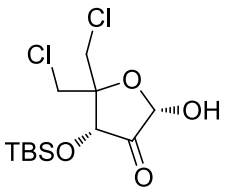
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (d, *J* = 0.7 Hz, 1H), 4.62 (d, *J* = 0.8 Hz, 1H), 3.79 (d, *J* = 11.8 Hz, 1H), 3.75 – 37.1 (m, 3H), 2.12 (s, 3H), 0.93 (s, 9H), 0.24 (s, 3H), 0.17 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 204.95, 169.48, 89.73, 84.36, 72.91, 46.37, 45.92, 25.75, 20.83, 18.25, -4.05, -5.08. **LRMS** [M+Na+MeOH$^+$] calc. for $C_{15}H_{28}Cl_2NaO_6Si$: 425.1, found: 425.3.



Lactone 2.41: $(COCl)_2$ was distilled at 45°C and reduced pressure prior to use, DMSO was standing over CaH_2 overnight, then distilled under reduced pressure into a dry flask containing 4A molecular sieves. Stock solutions of both reagents in dry DCM were prepared.

5.2 μL (60.4 μmol, 1 eq) $(COCl)_2$ was added as solution in 0.25 mL DCM into a dry round bottom flask under a N_2 atmosphere. Then the flask was cooled to -78°C and 6.4 μL (90.1 μmol, 1.5 eq) DMSO as a solution in 0.25 mL DCM was added. After stirring for 15 min at -78°C, 20 mg (60.4 μmol, 1 eq) **2.34** was added as a solution in 0.5 mL DCM and the reaction was maintained to stir for additional 45 min at -78°C. Afterwards, 18 mg (25 μL, 181 μmol, 3 eq) NEt_3 was added as a solution in 0.25 mL DCM. After 15 min at -78°C the reaction mixture was allowed to warm up to room temperature. After removal of all volatiles under reduced pressure, the residue was purified by flash chromatography (5 g SiOH, 5% EtOAc in cyclohexane, $KMnO_4$) giving **2.41** as colorless oil. No yield determined.

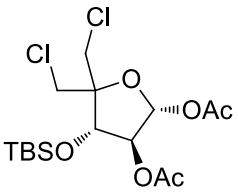
R_f = 0.3 (5% EtOAc in cyclohexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 3.82 (d, *J* = 12.1 Hz, 2H), 3.71 (d, *J* = 12.1 Hz, 2H), 0.95 (s, 9H), 0.19 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.13, 86.41, 44.31, 25.66, 18.34, -4.51. Two signals missing. **HRMS** [M+Na^+] calc. for $C_{12}H_{20}Cl_2NaO_3Si$: 333.0451, found: 333.0452.



Lactol *rac* 2.42: A dry roundbottom flask under a N_2 atmosphere was charged with 339 mg (1.02 mmol, 1 eq) diol **2.34** and subsequently dissolved in 10 mL dry DMSO. To the stirring solution, 315 mg (1.07 mmol, 1.05 eq) IBX was added in one scoop and the flask was then immersed into a preheated oil bath at 40°C. After 0.5 h, the solution was poured into a separation funnel containing 50 mL water and the mixture was extracted three times with 40 mL pentane. The combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure, giving 261 mg of crude ***rac* 2.42** which was used for the synthesis of ***rac* 2.35** without further purification.

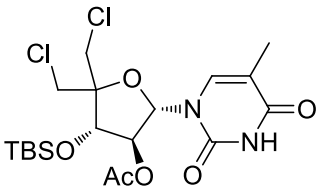
^{1}H NMR (500 MHz, DMSO) δ 5.12 (s, 1H), 4.68 (d, *J* = 0.8 Hz, 1H), 3.91 (d, *J* = 11.8 Hz, 1H), 3.87 (d, *J* = 11.9 Hz, 1H), 3.81 (d, *J* = 11.8 Hz, 1H), 3.78 (d, *J* = 11.8 Hz, 1H), 0.89 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H). **^{13}C NMR** (126 MHz, DMSO) δ 208.36 91.56, 80.39, 72.83, 47.07, 46.10, 25.26, 17.56, -3.88, -4.86. **HRMS** [M+Na+MeOH$^+$] calc. for $C_{13}H_{26}Cl_2NaO_5Si$: 383.1265, found: 383.1263.

Note: Consistent results up to a 1 g scale. Purification on SiOH resulted in smearing and elution of desired product over 6-8 CV. The resulting highly diluted fractions made spotting by $KMnO_4$ almost impossible. No UV absorption. This procedure requires further optimization and understanding of byproduct formations.



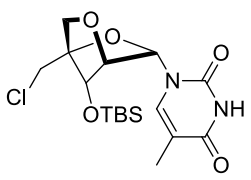
Diacetate *rac* 2.44b: A dry round bottom flask under a N_2 atmosphere was charged with 170 mg (458 μmol, 1 eq) ***rac* 2.35** as a solution in benzene. After evaporation of all volatiles, the residue was dissolved in 4.5 mL dry Et_2O before it was cooled to 0°C. To the stirring solution was then added 0.46 mL (6.3 mg, 458 μmol, 1 eq) 1M BH_3 in THF dropwise and stirring at this temperature was maintained for 2 h. Subsequently, 0.34 mL (4.58 mmol, 10 eq) acetone was added to quench the excess of BH_3, followed by 4.8 mL (50 mmol, 110 eq) Ac_2O and then 0.11 mL (1.37 mmol, 3 eq) pyridine. After complete addition, the solution was allowed to warm to room temperature and was kept stirring overnight. The contents were transferred into a bigger flask and diluted with 20 mL toluene. The resulting mixture was concentrated under reduced pressure and the procedure with toluene was repeated two more times. The crude product was purified by manual flash chromatography (25 g SiOH, 10% EtOAc in cyclohexane, $KMnO_4$, eluted in fractions 8-11 of 15 mL) giving 25 mg (13%, 60 μmol) of **2.44b** as colorless oil.

R_f = 0.15 (10% EtOAc in cyclohexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.40 (d, *J* = 4.6 Hz, 1H), 5.12 (dd, *J* = 7.3, 4.6 Hz, 1H), 4.60 (d, *J* = 7.3 Hz, 1H), 3.85 (d, *J* = 11.3 Hz, 1H), 3.82 (d, *J* = 12.2 Hz, 1H), 3.73 (d, *J* = 12.3 Hz, 1H), 3.62 (d, *J* = 11.4 Hz, 1H), 2.09 (s, 3H), 2.09 (s, 3H), 0.89 (s, 9H), 0.16 (s, 3H), 0.11 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.71, 169.11, 92.44, 84.08, 78.36, 76.96, 46.51, 45.68, 25.71, 21.19, 20.53, 18.05, -4.26, -4.89. **HRMS** [M+Na^+] calc. for $C_{16}H_{28}Cl_2NaO_6Si$: 437.0924, found: 437.0923.



Thymin *rac* 2.45b: Adapted from Lumholt.[66] A small screw cap vial, dry and under a N_2 atmosphere sealed with a septum, was charged with 12 mg (29 μmol, 1 eq) diacetate **2.44b** as a solution in benzene. After evaporation of all volatiles, the residue was dissolved in 0.3 mL dry MeCN before 4.3 mg (35 μmol, 1.2 eq) thymin and then 22 μL (18.2 mg, 81 μmol, 2.8 eq) BSA were added. The stirring solution was then heated to 80°C for 1 h (MeCN is prone to leave the reaction vessel at that scale and temperature, so the nitrogen flow was stopped), subsequently 7 μL (38 μmol 1.3 eq) TMS-OTf dissolved in 43 μL DCM was added dropwise. The reaction was maintained at 80°C for another 6.5 h before it was allowed to cool to room temperature and 1 mL DCM was added. A single wash with an equal amount of aqueous saturated $NaHCO_3$ was done in a syringe and after separation of the layers the organic fraction was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by manual flash chromatography (5 g SiOH, 30% EtOAc in cyclohexane, 254 nm, eluted in fractions 6-10 of 5 mL) giving 13 mg (93%, 27 μmol) of **2.45b** as white solid in a 10:1 mixture of diastereomers. Residual EtOAc after flashing was removed by co-evaporation with $CHCl_3$.

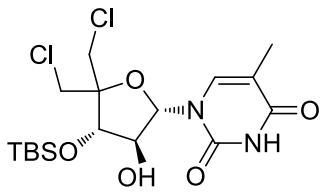
R_f = 0.2 (30% EtOAc in cyclohexane).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.40 (d, *J* = 1.3 Hz, 1H), 6.16 (d, *J* = 3.4 Hz, 1H), 5.11 (dd, *J* = 3.4, 2.4 Hz, 1H), 4.44 (d, *J* = 2.4 Hz, 1H), 3.92 (d, *J* = 11.8 Hz, 1H), 3.87 (d, *J* = 11.7 Hz, 1H), 3.86 (d, *J* = 11.7 Hz, 1H), 3.75 (d, *J* = 11.8 Hz, 1H), 2.16 (s, 3H), 1.94 (d, *J* = 1.2 Hz, 3H), 0.93 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.43, 163.16, 150.07, 135.17, 112.06, 88.20, 87.68, 82.83, 77.36, 43.96, 43.29, 25.80, 20.82, 18.11, 12.76, -4.49, -5.26. **HRMS** [M+Na^+] calc. for $C_{19}H_{30}Cl_2N_2NaO_6Si$: 503.1142, found: 503.1145.



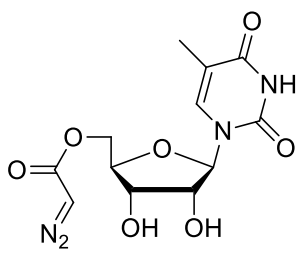
Bicycle 2.46b: Adapted from Lumholt.[66] A small screw cap vial, dry and under a N_2 atmosphere sealed with a septum, was charged with 4 mg (8.31 μmol, 1 eq) **2.45b** which was subsequently dissolved in 0.2 mL dioxane. Then 0.1 mL of water was added that led to immediate precipitation. Subsequently 71 μL (141 μmol, 17 eq) 2M aqueous NaOH solution was added and the resulting solution was stirred at room temperature for 1 h before it was transferred into another vial containing 1 mL saturated aqueous NH_4Cl. After a single extraction with DCM in a syringe and after separation of the layers, the organic fraction was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 3.5 mg of a white solid. 1H NMR analysis suggested the absence of starting material **2.46b** and the formation of the two new products **2.46b** and **2.47b** in a ratio of 1:5.

In order to obtain more of the desired bicycle **2.46b**, the crude sample mixture was added into an oven-dried NMR tube and dissolved in 0.4 mL DMSO-d_6. Upon addition of 6 μL (48 μmol, 6 eq) DBU (exact addition of DBU was not possible due to its high viscosity) and 6 mg (40 μmol, 5 eq) NaI, the tube was shaken for 2 minutes and then immersed into a preheated oil bath at 90°C overnight. Measuring of the sample revealed a conversion to a 1:1 mixture. Accordingly, the DMSO solution was injected into the preparative HPLC (MeCN / 0.1% TFA in H_2O, 10% - 90% over 20 minutes, t_R = 17 min, 254 nm) and 0.6 mg (17%, 1.41 μmol) **2.46b** was isolated as white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.44 (q, *J* = 1.1 Hz, 1H), 5.68 (s, 1H), 4.48 (d, *J* = 2.2 Hz, 1H), 4.27 (d, *J* = 2.2 Hz, 1H), 4.17 (d, *J* = 8.5 Hz, 1H), 3.95 (d, *J* = 8.6 Hz, 1H), 3.86 (d, *J* = 12.4 Hz, 1H), 3.84 (d, *J* = 12.4 Hz, 1H), 1.91 (d, *J* = 1.2 Hz, 3H), 0.82 (s, 9H), 0.09 (s, 3H), 0.01 (s, 3H). **^{13}C NMR** (126 MHz, HMBC/HMQC, $CDCl_3$) δ 149.62, 163.27, 136.42, 108.35 89.37, 88.55, 77.90, 74.25, 72.83, 38.03, 25.42, 18.02, 12.73, -4.95, -5.30. **HRMS** [M+Na^+] calc. for $C_{17}H_{27}ClN_2NaO_5Si$: 425.1270, found: 425.1274.

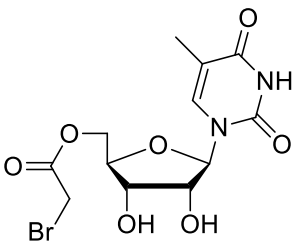


Alcohol 2.47b: 1H NMR (400 MHz, $CDCl_3$) δ 9.58 (s, 1H), 7.48 (d, *J* = 1.2 Hz, 1H), 5.84 (d, *J* = 2.1 Hz, 1H), 4.37 (d, *J* = 2.3 Hz, 1H), 4.23 (t, *J* = 2.2 Hz, 1H), 4.03 (d, *J* = 11.6 Hz, 1H), 3.99 (d, *J* = 11.7 Hz, 1H), 3.93 (d, J = 12.0 Hz, 1H), 3.90 (d, *J* = 12.0 Hz, 1H), 1.93 (d, *J* = 1.0 Hz, 4H), 0.85 (s, 16H), 0.07 (s, 3H), -0.00 (s, 3H). **LRMS** [M+Na^+] calc. for $C_{17}H_{28}Cl_2N_2NaO_5Si$: 461.1, found: 461.3.



Diazo acetate 2.49: General methodology by Fukuyama.[75] A dry round bottom flask under a N_2 atmosphere was charged with 20 mg (52.7 μmol, 1 eq) **2.52** which was suspended in 1 mL dry THF, before 18 mg (52.7 μmol, 1 eq) TsNH-NHTs[75] was added. 34 μL (264 μmol, 5 eq) DBU was added dropwise at room temperature and the slurry stirred for 1 h. The resulting emulsion was decanted, the remaining oil mixed with 2 mL THF, stirred and then decanted again. The combined THF fractions were concentrated under reduced pressure and dissolved in DMSO to purify by preparative HPLC (MeCN / H_2O, 5-30% over 20 min, t_R = 12 min, 254 nm) giving 5 mg (29%, 15.3 μmol) of desired diazo acetate **2.49**. The compound was highly hygroscopic and formed an oil. After suspending in toluene, sonication and subsequent concentration a white solid was obtained.

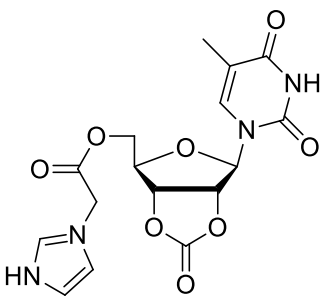
^{1}H NMR (400 MHz, DMSO) δ 11.35 (s, 1H), 7.38 (d, *J* = 0.9 Hz, 1H), 5.77 (d, *J* = 5.6 Hz, 1H), 5.68 (s br, 1H, CH-N_2), 5.43 (d, *J* = 5.8 Hz, 1H), 5.28 (d, *J* = 5.2 Hz, 1H), 4.35 (dd, *J* = 11.9, 3.2 Hz, 1H), 4.24 (dd, *J* = 12.0, 5.5 Hz, 1H), 1.10 – 4.03 (m, 1H), 4.00 – 3.93 (m, 2H), 1.80 (d, *J* = 0.8 Hz, 2H). **^{13}C NMR** (101 MHz, DMSO) δ 172.35 (HMBC only), 163.65, 150.71, 136.10, 109.81, 88.00, 81.22, 72.32, 69.88 (2C), 64.15, 12.05. **HRMS** [M+Na^+] calc. for $C_{12}H_{14}N_4NaO_7$: 349.0755, found: 349.0752.



Bromo acetate 2.52: General methodology by Fukuyama.[75] A dry round bottom flask under a N_2 atmosphere was charged with 4.25 g (16 mmol, 1 eq) 5-methyl uridine which was subsequently suspended in 100 mL dry MeCN. Then 4.15 g (49 mmol, 3 eq) $NaHCO_3$ was added and the suspension was cooled to 0°C before 2.87 mL (6.64 g, 33 mmol, 2 eq) bromoacetyl bromide was added dropwise. Cooling was then removed and the suspension stirred overnight. After filtration through a sintered glass frit (filter cake was rinsed once with MeCN), crude **2.52** was obtained in 75% purity containing 25% starting material and was used without further purification if not stated else in the upcoming procedures.

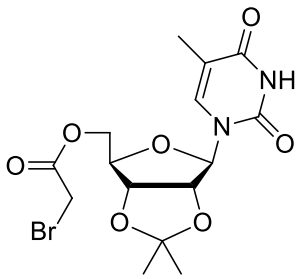
An analytical sample was obtained by preparative HPLC (MeCN / 0.1% TFA in H_2O, 5% - 30% over 20 min, t_R = 14 min, 254 nm).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 7.37 (d, *J* = 1.1 Hz, 1H), 5.84 (d, *J* = 4.4 Hz, 1H), 4.54 – 4.42 (m, 2H), 4.37 – 4.30 (m, 2H), 4.24 (t, *J* = 5.2 Hz, 1H), 3.91 (s, 2H), 1.90 (d, *J* = 0.8 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO) δ 167.10, 163.67, 150.73, 136.24, 109.84, 88.06, 80.92, 72.24, 69.73, 65.44, 27.02, 12.09. **HRMS** [M+Na^+] calc. for $C_{12}H_{15}BrN_2NaO_7$: 400.9955, found: 400.9951.



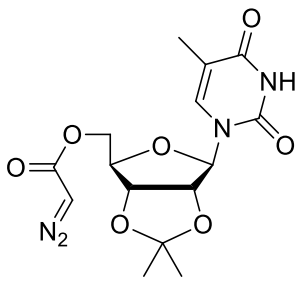
Imidazole 2.53: A dry round bottom flask under a N_2 atmosphere was charged with 10 mg (26.4 μmol, 1 eq) **2.52** and suspended in 1 mL dry MeCN before 9 mg (52.7 μmol, 2 eq) CDI was added in one scoop. After 21 h all volatiles were removed under reduced pressure. The residue was dissolved in DMSO and purified by preparative HPLC (MeCN / H_2O, 5-40% over 20 min, t_R = 8 min, 254 nm) giving 3 mg (28%, 7.39 μmol) of **imidazole 2.53** as white solid. The corresponding signals were not observed in aliquot NMR spectra. It is thus suggested that the product formed during concentration or purification of the sample.

^{1}H NMR (400 MHz, DMSO) δ 11.55 (s, 1H), 9.00 (s, 1H), 7.67 (d, *J* = 7.6 Hz, 2H), 7.65 (d, *J* = 1.1 Hz, 1H), 5.95 (d, *J* = 1.8 Hz, 1H), 5.65 (dd, *J* = 7.7, 1.9 Hz, 1H), 5.34 (dd, *J* = 7.7, 3.9 Hz, 1H), 5.25 (s, 2H), 4.58 – 4.47 (m, 2H), 4.36 (dd, *J* = 12.7, 8.4 Hz, 1H), 1.77 (d, *J* = 1.0 Hz, 3H). **^{13}C NMR** (101 MHz, DMSO) δ 166.87, 163.92, 153.45, 150.41, 139.39, 136.85, 123.21, 120.10, 109.64, 92.84, 83.44, 82.60, 79.73, 65.02, 49.10, 11.88. **HRMS** [M+H$^+$] calc. for $C_{16}H_{17}N_4O_8$: 393.1041, found: 393.1038.



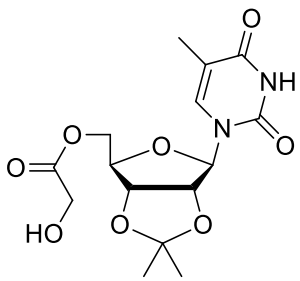
Dimethyl ketal 2.54: In a round bottom flask, 3.12 g (8.23 mmol, 1 eq) crude **2.52** was stirred with 40.3 mL (329 mmol, 40 eq) 2,2-dimethoxy propane, 207 mg (823 μmol, 0.1 eq) PPTS in 9 mL DMF for 24 h. The slurry was then decanted and the residue was taken up with DCM and filtered. The combined liquids were subsequently concentrated under reduced pressure and the DMF solution was applied on a reverse phase Isolera column in 4-5 mL batches: 60 g C18 reverse phase silica, MeCN / H_2O, 0-60% over 13 CV, elutes after 9-10 CV, 254 nm. After lyophilization 2.38 g (69%, 7.32 mmol) of **2.54** was obtained as sticky white solid. Hygroscopic!

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.07 (d, *J* = 1.2 Hz, 1H), 5.61 (d, *J* = 2.1 Hz, 1H), 5.03 (dd, *J* = 6.5, 2.1 Hz, 1H), 4.85 (dd, *J* = 6.5, 4.1 Hz, 1H), 4.49 – 4.31 (m, 3H), 3.88 (s, 2H), 1.93 (d, *J* = 1.1 Hz, 3H), 1.57 (s, 3H), 1.35 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.88, 163.61, 149.97, 138.39, 114.90, 111.40, 95.01, 84.98, 84.37, 81.09, 65.69, 27.28, 25.61, 25.43, 12.50. **HRMS** [M+Na$^+$] calc. for $C_{15}H_{19}BrN_2NaO_7$: 441.0268, found: 441.0270. **$[\alpha]_D^{20}$** + 7.4 (c 1.20, $CHCl_3$).



Diazo acetate 2.55: General methodology by Fukuyama.[75] A dry round bottom flask under a N_2 atmosphere was charged with 1 g (2.39 mmol, 1 eq) dimethyl ketal **2.54** which was dissolved in 24 mL dry THF. 1.62 g (4.77 mmol, 2 eq) TsNH-NHTs[75] was added before the mixture was cooled to 0°C and 1.54 mL (1.82 g, 11.9 mmol, 5 eq) DBU was added dropwise. It was stirred at 0°C for 10 min and then allowed to warm up to room temperature where it was stirred for another 20 min. Precipitation was observed. Then, all volatiles were removed under reduced pressure and dissolved in DMSO to apply a on reverse phase Isolera column: 60 g C18 reverse phase silica, MeCN / H_2O, 0-60% over 13 CV, elutes after 7-9 CV, 254 nm. After lyophilization 760 mg (89%, 2.13 mmol) of **2.55** was obtained as pale yellow solid. Slightly hygroscopic.

^{1}H NMR (400 MHz, CD_3CN) δ 9.02 (s br, 1H), 7.20 (d, *J* = 1.2 Hz, 1H), 5.74 (d, *J* = 2.5 Hz, 1H), 5.02 (s br, 1H, CH-N_2), 4.91 (dd, *J* = 6.5, 2.5 Hz, 1H), 4.78 (dd, *J* = 6.5, 3.5 Hz, 1H), 4.39 (dt, *J* = 8.2, 5.8 Hz, 1H), 4.29 (dd, *J* = 5.7, 2.2 Hz, 1H), 4.26 (dd, *J* = 5.7, 2.3 Hz, 1H), 1.82 (d, *J* = 1.2 Hz, 3H), 1.52 (s, 3H), 1.34 – 1.28 (m, 3H). **^{13}C NMR** (101 MHz, CD_3CN) δ 167.31 (HMBC only), 164.53, 151.22, 138.30, 115.00, 111.30, 93.61, 85.24, 85.19, 81.77, 65.10, 47.07 (C=N_2, weak), 27.30, 25.46, 12.34. **HRMS** [M+Na^+] calc. for $C_{15}H_{18}N_4NaO_7$: 389.1068, found: 389.1066. **$[\alpha]_D^{20}$** + 4.9 (c 0.70, $CHCl_3$).

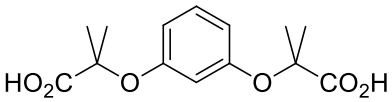


Alcohol 2.57: General procedure for the attempted lactone formation via C-H insertion (Table 2-4): A dry round bottom flask under a N_2 atmosphere was charged with 20 mg (54.6 μmol, 1 eq) diazo acetate **2.55** to which 1 mL dry benzene was added and subsequently removed under high vacuum. Then again 1 mL dry benzene was added and removed before the obtained solid was dissolved in 1 mL dry DCM. In a separate dry round bottom flask under a N_2 atmosphere, a solution or suspension of the respective Rh(II) catalyst was made. 10 mol% Rh regarding starting material **2.55** in 1 mL DCM, was then transferred over 30 min to the stirring solution of **2.55** at different temperatures (Table 2-4). After stirring for 1h all volatiles were removed under reduced pressure and redissolved in DMSO to inject into the preparative HPLC (MeCN / H_2O, 5% - 60% over 20 minutes, t_R = 14 min, 254 nm) to yield **2.57** as the major product.

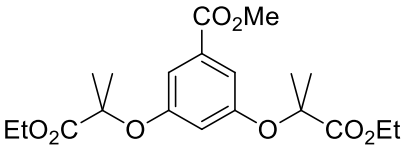
^{1}H NMR (400 MHz, DMSO) δ 11.42 (s, 1H), 7.52 (d, *J* = 1.2 Hz, 1H), 5.81 (d, *J* = 2.4 Hz, 1H), 5.39 (t, *J* = 6.6 Hz, 1H), 5.00 (dd, *J* = 6.4, 2.4 Hz, 1H), 4.80 (dd, *J* = 6.4, 4.0 Hz, 1H), 4.32 – 4.17 (m, 3H), 4.07 (dd, *J* = 14.8, 4.2 Hz, 1H), 4.01 (dd, *J* = 14.8, 4.2 Hz, 1H), 1.77 (d, *J* = 1.0 Hz, 3H), 1.49 (s, 3H), 1.29 (s, 3H). **^{13}C NMR** (101 MHz, DMSO) δ 172.35, 163.80, 150.31, 138.01, 113.40, 109.69, 91.49, 83.51, 83.29, 80.48, 63.79, 59.57, 26.98, 25.19, 11.93. **HRMS** [M+Na^{+}] calc. for $C_{15}H_{21}N_2NaO_8$: 379.1112, found: 379.1109.

5.4 Rhodium: ligands, complexes and applications

5.4.1 Synthesis of carboxylate ligands

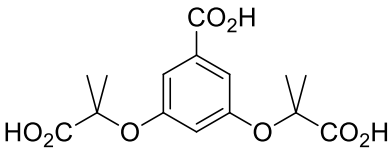


The synthesis and spectroscopic characterization of **diacid** (**3.10a**) has been described by Bonar-Law and co-workers.[101]



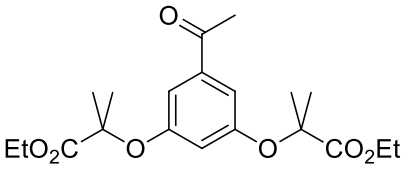
Triester 3.9b: A round bottom flask was charged with 840 mg (5.0 mmol, 1 eq) methyl 3,5-dihydroxybenzoate and was dissolved in 12 mL DMF, then 2.76 g (20 mmol, 4 eq) K_2CO_3, 1.63 g (5.0 mmol, 1 eq) Cs_2CO_3 and 3.72 mL (25 mmol, 5 eq) Ethyl 2-bromoisobutyrate were added. The mixture was stirred at 80°C for 24 h, was then allowed to cool to room temperature and poured into 50 mL water and extracted three times with 20 mL Et_2O. The organic phase was consecutively washed with 10 mL 1M aqueous HCl, 20 mL water, dried over Na_2SO_4, filtered and evaporated under reduced pressure. In order to remove the excess of ethyl 2-bromoisobutyrate the oil was heated to 50°C under high vacuum for 2 h, giving 1.63 g (82%, 4.1 mmol) **3.9b** as pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.17 (d, *J* = 2.3 Hz, 2H), 6.59 (t, *J* = 2.3 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 4H), 3.86 (s, 3H), 1.58 (s, 12H), 1.26 (t, *J* = 7.1 Hz, 6H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ: 173.9, 166.5, 156.3, 131.5, 115.4, 114.3, 79.8, 61.7, 52.4, 25.5, 14.2. **HRMS** [M+Na^+] calc. for $C_{20}H_{28}NaO_8$: 419.1677, found: 419.1676.



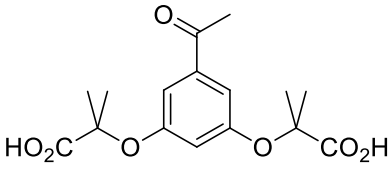
Triacid 3.10b: A round bottom flask was charged with 300 mg (757 μmol, 1 eq) **3.9b** and was dissolved in 5 mL THF, then 5 mL H_2O was added which resulted in a milky suspension. 953 mg (230 mmol, 30 eq) LiOH x H_2O was added in one scoop and the mixture was heated to 60°C for 20 h. After cooling to room temperature 13 mL of 2 M aqueous HCl was added slowly and the mixture was transferred into a separation funnel. It was extracted 3 times with 20 ml of EtOAc and the combined phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to obtain a yellow oil. The crude product was then applied as a solution in 3 mL DMSO on a 50 g C-18 reverse phase column and eluted with an Isolera Four (H_2O / MeCN, 5%-40% over 11 CV, eluted after 9 CV). After lyophilization, 190 mg (77%, 583 μmol) triacid **3.10b** was obtained as a white semi solid.

^{1}H-NMR (400 MHz, MeOD) δ: 7.20 (d, *J* = 2.3 Hz, 2H), 6.67 (s, 1H), 1.58 (s, 12H). **^{13}C-NMR** (101 MHz, MeOD) δ: 177.3, 157.6, 133.3, 115.8, 115.0, 80.6, 25.7 (one carbon missing). **HRMS** [M+Na^+] calc. for $C_{15}H_{18}NaO_8$: 349.0895, found: 349.0894.



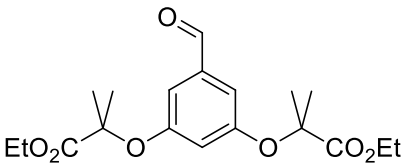
Ketone 3.9c: A roundbottom flask was charged with 380 mg (2.5 mmol, 1 eq) 3,5-dihydroxyacetophenone and was dissolved in 6 mL DMF. Then 1.38 g (10 mmol, 4 eq) K_2CO_3, 800 mg (2.5 mmol, 1 eq) Cs_2CO_3 and 1.86 mL (12 mmol, 5 eq) Ethyl 2-bromoisobutyrate were added. The mixture was stirred at 80°C overnight, was then allowed to cool to room temperature and poured into 50 mL water and extracted three times with 20 mL Et_2O. The organic phase was consecutively washed with, 20 mL water, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The resulting brown oil was purified by flash chromatography (hexane/EtOAc 6:1) and 775 mg (81%, 2.04 mmol) **3.9c** was isolated as colorless oil.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.08 (d, *J* = 2.2 Hz, 2H), 6.55 (t, *J* = 2.2 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 4H), 2.51 (s, 3H), 1.59 (s, 12H), 1.26 (t, *J* = 7.2 Hz, 6H). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ: 197.2, 173.9, 156.5, 138.6, 114.7, 113.0, 79.7, 61.8, 26.8, 25.5, 14.2. **HRMS** [M+Na^+] calc. for $C_{20}H_{28}NaO_7$: 403.1728, found: 403.1727.



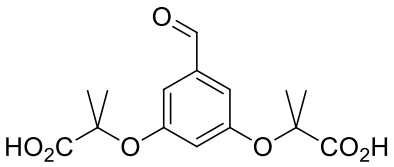
Diacid 3.10c: A round bottom flask was charged with 330 mg (0.86 mmol, 1 eq) **3.9c** and was dissolved in 4 mL MeOH, then 2 mL of a solution containing 300 mg (12.5 mmol, 15 eq) LiOH x H_2O in 2 mL water was added. After heating the mixture for 3 h at 60°C it was allowed to cool to room temperature and the reaction mixture was poured into 20 mL 1M aqueous HCl and extracted three times with 20 mL EtOAc. The combined organic phases were washed with 20 mL water, dried over Na_2SO_4, filtered and evaporated under reduced pressure to give 280 mg (99%, 0.86 mmol) **3.10c** as colourless crystals.

^{1}H-NMR (500 MHz, DMSO-d_6) δ: 13.21 (s, 2H), 7.01 (d, *J* = 2.3 Hz, 2H), 6.50 (t, *J* = 2.2 Hz, 1H), 2.49 (s, 3H), 1.52 (s, 12H). **^{13}C-NMR** (126 MHz, DMSO-d_6) δ: 174.7, 156.2, 122.4, 111.0, 99.5, 97.4, 78.9, 26.7, 25.0. **HRMS** [M+Na^+] calc. for $C_{16}H_{20}NaO_7$: 347.1102, found: 347.1101.



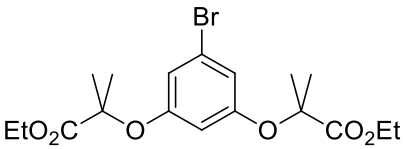
Aldehyde 3.9d: A round bottom flask was charged with 345 mg (2.5 mmol, 1 eq) 3,5-Dihydroxybenzaldehyde and was dissolved in 6 mL DMF, then 1.38 g (10 mmol, 4 eq) K_2CO_3, 800 mg (2.5 mmol, 1 eq) Cs_2CO_3 and 1.86 mL (12 mmol, 5 eq) Ethyl 2-bromoisobutyrate were added. The mixture stirred at 80°C overnight and was then allowed to cool to room temperature and poured into 50 mL water and extracted three times 20 mL Et_2O. The organic phase was consecutively washed with 10 mL 1M aqueous HCl, 20 mL water, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The resulting brown oil was purified by flash chromatography (hexane/EtOAc 6:1) and 525 mg (56%, 1.4 mmol) **3.9d** was isolated as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.83 (s, 1H), 6.97 (d, *J* = 2.3 Hz, 2H), 6.64 (t, *J* = 2.3 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 4H), 1.60 (s, 12H), 1.25 (t, *J* = 7.1 Hz, 6H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ: 191.4, 173.8, 157.0, 138.0, 116.3, 113.7, 79.9, 61.8, 25.5, 14.2. **HRMS** [M+Na$^+$] calc. for $C_{19}H_{26}NaO_7$: 389.1576, found: 389.1571.



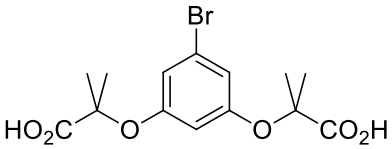
Diacid 3.10d: A round bottom flask was charged with 525 mg (1.4 mmol, 1 eq) **3.9d** and was dissolved in 4 mL MeOH, then 2 mL of a solution containing 300 mg (12.5 mmol, 9 eq) LiOH x H_2O in 2mL water was added. After heating the mixture for 3 h at 60°C a TLC control (5% MeOH/EtOAc) indicated full conversion of the diester. The reaction mixture was poured into 20 mL 1M aqueous HCl and extracted three times with 20 mL EtOAc. The combined organic phases were washed with 20 mL water, dried over Na_2SO_4, filtered and evaporated under reduced pressure to give 345 mg (79%, 1.1 mmol) **3.10d** as yellow oil.

^{1}H-NMR (400 MHz, CD_2Cl_2) δ: 9.85 (s, 1H), 7.08 (d, *J* = 2.2 Hz, 2H), 6.59 (t, *J* = 2.2 Hz, 1H), 1.61 (s, 12H). **^{13}C-NMR** (101 MHz, CD_2Cl_2) δ: 191.8, 178.4, 156.9, 139.0, 115.4, 114.6, 80.1, 25.6. **HRMS** [M+Na$^+$] calc. for $C_{15}H_{18}NaO_7$: 333.0950, found: 333.0945.



Bromide 3.9e: 200 mg (1.06 mmol, 1 eq) 3-Bromoresorcinol and 0.78 mL (5.29 mmol, 5 eq) ethyl 2-bromoisobutyrate were dissolved in 3 mL dry DMF in a dry round bottom flask under a N_2 atmosphere. Then, 585 mg (4.23 mmol, 4 eq) K_2CO_3 and 345 mg (1.06 mmol, 1 eq) Cs_2CO_3 were added. The slurry was subsequently immersed into a preheated oil bath at 80°C and stirred vigorously for 22 h. After cooling to room temperature the mixture was poured into a separation funnel containing 25 mL of water and was extracted 3 times with 20 mL of Et_2O. The combined organics were then washed once with 10 mL of aqueous 1M HCl and once with 20 mL of water, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The yellow oil was purified by flash chromatography (cyclohexane/EtOAc 9:1). After concentration of the collected fractions 211 mg (48%, 0.51 mmol) diester **3.9e** was isolated as colourless oil.

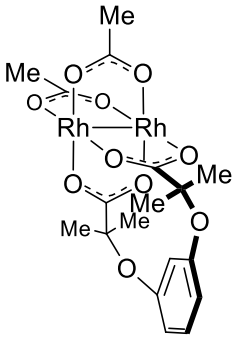
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (d, *J* = 2.2 Hz, 2H), 6.28 (t, *J* = 2.2 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 4H), 1.56 (s, 12H), 1.26 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.81, 156.82, 122.05, 116.56, 109.16, 79.83, 61.75, 25.48, 14.18. **HRMS** [M+Na$^+$] calc. for $C_{18}H_{25}BrNaO_8$: 439.0727, found: 439.0726.



Diacid 3.10e: A round bottom flask was charged with 103 mg (0.247 mmol, 1 eq) **3.9e** and was dissolved in 1.5 mL THF, then 1.5 mL H_2O was added which resulted in a milky suspension. 207 mg (4.94 mmol, 20 eq) LiOH x H_2O was added in one scoop and the mixture was heated to 60°C for 13h. After cooling to room temperature 3 mL of aqueous 2M HCl were added slowly and the mixture was transferred into a separation funnel. It was extracted 3 times with 10 mL of EtOAc and the combined phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to obtain a yellow oil. The crude product was then applied as a solution in 3 mL DMSO on a 50 g C-18 reverse phase column and eluted with an Isolera Four (MeCN in H_2O, gradient 5%-40% over 8 CV, elutes after 3 CV). After lyophilisation, 89 mg (84%, 0.207 mmol) diacid **3.10e** was obtained as a colorless oil.

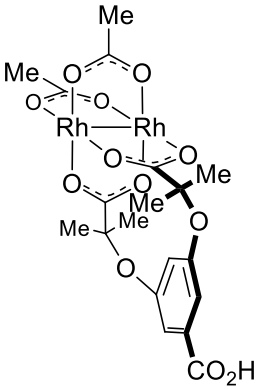
^{1}H NMR (400 MHz, MeOD) δ 6.70 (d, *J* = 2.1 Hz, 2H), 6.39 (t, *J* = 2.2 Hz, 1H), 1.56 (s, 12H). **^{13}C NMR** (101 MHz, MeOD) δ 177.1, 158.3, 122.8, 117.2, 110.0, 80.8, 25.7. **HRMS** [M+Na$^+$] calc. for $C_{14}H_{17}BrNaO_6$: 383.0101, found: 383.0104.

5.4.2 Synthesis of dirhodium carboxylate catalysts



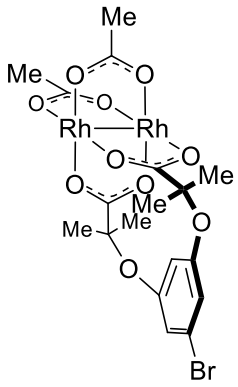
The synthesis and spectroscopic characterization of dirhodium dicarboxylate (**3.1**) has been described by Bonar-Law and co-workers.[174]

Rh complex 3.1: A dry round bottom flask under a N_2 atmosphere was charged with 155.7 mg (0.348 mmol, 1 eq) $Rh_2(OAc)_4$ and 98.2 mg (0.348 mmol, 1 eq) **3.10a** which were then dissolved in 15.6 mL *N*,*N*-dimethyl aniline. The mixture was stirred at 140°C for 3 h and the reaction mixture was allowed to cool down to room temperature and transferred into a separation funnel containing 50 mL DCM and 3 mL MeCN. In order to remove excess of aniline, the organic phase was extracted three times with 90 mL 2M aqueous HCl and finally washed twice with 100 mL H_2O. After drying over Na_2SO_4 and filration, the organic phase was removed under reduced pressure to give a blue colored residue. Gradient chromatograpy of the oil on 17 g of silica gel eluted first (DCM/EtOAc: 95:5) bis- adduct **3.5** (23 mg, 0.03 mmol, 10%) followed by **3.1** after change of the gradient (DCM/EtOAc: 90:10). Combined fractions of the desired bright-green fractions gave 125 mg (60%, 0.21 mmol) **3.1** as green solid.



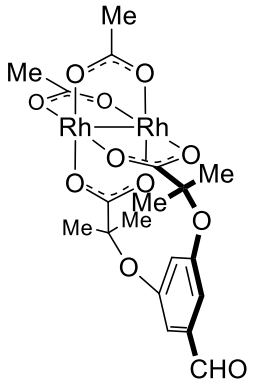
Rh complex 3.2: A dry round bottom flask under a N_2 atmosphere was charged with 30 mg (0.055 mmol, 1 eq) $Rh(OAc)_2(TFA)_2$[175] and subsequently dissolved in 3 mL 1,2-dichloroethane. Then, 18 mg (0.055 mmol, 1 eq) triacid **3.10b** was added, followed by a dropwise addition of 0.6 mL dry EtOAc to dissolve the ligand. Sometimes sonication was necessary in order to completely dissolve the ligand. The green/blue solution was then immersed into a preheated oil bath at 60°C and stirred for 16 h. After cooling to room temperature, all volatiles were removed under reduced pressure and the solid was dissolved in 1 mL of DMSO. The solution was injected into the preparative HPLC (MeCN / 0.1% TFA in H_2O, 2% to 50% over 28 min. t_R = 26 min) and the product eluted as a purple liquid. After lyophilization, 11 mg (31%, 0.017 mmol) **3.2** were obtained as green solid.

^{1}H NMR (400 MHz, 5 % v/v MeOD in CD_2Cl_2) δ 7.16 (d, *J* = 2.3 Hz, 2H), 6.20 (t, *J* = 2.3 Hz, 1H), 1.87 (s, 6H), 1.37 (s, 12H). **^{13}C NMR** (101 MHz, 5 % v/v MeOD in CD_2Cl_2) δ 192.9, 192.0, 168.4, 156.4, 132.4, 116.9, 114.1, 81.4, 25.1, 23.7. **HRMS** [M+Na$^+$] calc. for $C_{19}H_{22}NaO_{12}Rh_2$: 670.9119, found: 670.9112.



Rh complex 3.3: A dry round bottom flask under a N_2 atmosphere was charged with 20 mg (0.055 mmol, 1 eq) **3.10e** as a solution in EtOAc and all volatiles were subsequently removed under reduced pressure. Then 2 mL of 1,2-dichloroethane were added, followed by 30 mg (0.055 mmol, 1 eq) $Rh(OAc)_2(TFA)_2$[175]. The green solution was immersed into a preheated oil bath at 60°C and stirred for 7h. At this time most of the ligand was consumed and the amount of byproducts was lowest compared to desired complex **3.3**. After cooling to room temperature, all volatiles were removed under reduced pressure. The obtained green solid was subsequently dissolved in 1 mL of DMSO and injected into the preparative HPLC (MeCN / 0.1% TFA in H_2O, 2% to 70% over 28 min. t_R = 27 min, 254 nm) and the product eluted as a purple liquid. After lyophilization, 10 mg (27%, 0.015 mmol) of **3.3** were obtained as green solid. 3 mg of $Rh_2(OAc)_2(TFA)_2$ (t_R = 26 min) were re-isolated.

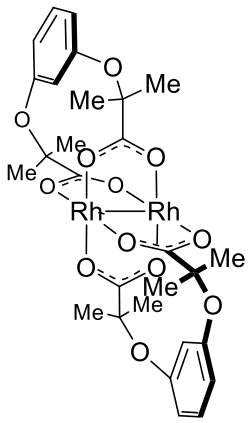
^{1}H NMR (500 MHz, 5 % v/v MeOD in $CDCl_3$) δ 6.67 (d, *J* = 2.1 Hz, 2H), 5.93 (t, *J* = 2.1 Hz, 1H), 1.89 (s, 6H), 1.36 (s, 12H). **^{13}C NMR** (126 MHz, 5 % v/v MeOH in $CDCl_3$) δ 192.5, 191.7, 156.4, 121.8, 118.1, 107.7, 81.1, 25.0, 23.6. **HRMS** [M+Na$^+$] calc. for $C_{18}H_{21}BrNaO_{10}Rh_2$: 704.8320, found: 704.8311.



$Rh_2(OAc)_2(TFA)_2$ was prepared according to Lou[175]

Rh complex 3.4: A dry round bottom flask under a N_2 atmosphere was charged with 23 mg (0.073 mmol, 1 eq) **3.10d** as a solution in EtOAc and all volatiles were subsequently removed under reduced pressure. Then 12 ml of 1,2-dichloroethane were added and followed by 80 mg (0.15 mmol, 2 eq) $Rh(OAc)_2(TFA)_2$. The green-blue solution was immersed into a preheated oil bath at 70°C and stirred for 2 h. ^{1}H NMR aliquot suggested full conversion of the ligand. Thus, all volatiles were removed under reduced pressure and the residual green solid dissolved in 2 mL of DMSO to inject it in the preparative HPLC (MeCN / 0.1% TFA in H_2O, 2% to 70% over 25 min, t_R = 23 min, 254 nm) and the product eluted as a purple liquid. After lyophilization, 16 mg (35%, 0.025 mmol) of **3.4** were obtained as green solid. 27 mg of excess $Rh_2(OAc)_2(TFA)_2$ (t_R = 26 min) were re-isolated.

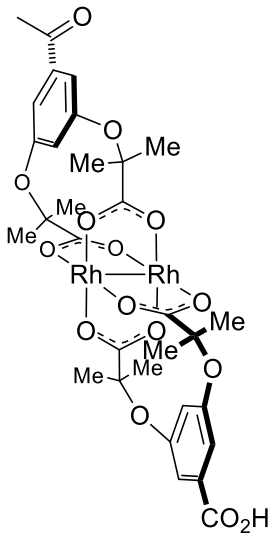
^{1}H NMR (400 MHz, 5 % v/v MeOD in CD_2Cl_2) δ 9.83 (s, 1H), 7.00 (d, *J* = 2.2 Hz, 2H), 6.22 (t, *J* = 2.2 Hz, 1H), 1.87 (s, 6H), 1.39 (s, 12H). **^{13}C NMR** (101 MHz, 5 % v/v MeOD in CD_2Cl_2) δ 192.8, 192.2, 192.0, 157.1, 138.5, 116.2, 115.1, 81.6, 25.2, 23.7. **HRMS** [M+Na$^+$] calc. for $C_{19}H_{22}NaO_{11}Rh_2$: 654.9164, found: 654.9163.



Dirhodium tetracarboxylate 3.5 was synthesized according to the synthesis protocol of Espino *et* al.[176]

The chelate was synthesized by reacting 50 mg (76 μmol, 1 eq) $Rh_2(O_2CCF_3)_4$ with six equivalent portions of diacid **3.10a** (43 mg, 152 μmol in total, 2 eq) in 1.5 mL 1,2-dichloroethane at 130°C for a total of 3 h. A TLC control (cyclohexane/EtOAc 1:1) indicated full conversion of the $Rh_2(O_2CCF_3)_4$. The solvent was removed under reduced pressure to give a green solid (80 mg) which was purified by flash chromatography (cyclohexane/EtOAc 9:1). First, 12 mg (16 μmol) of the mono substituted chelate was isolated as green solid, followed by 46 mg (78%, 60 μmol) dirhodium tetracarboxylate **3.5** as green solid.

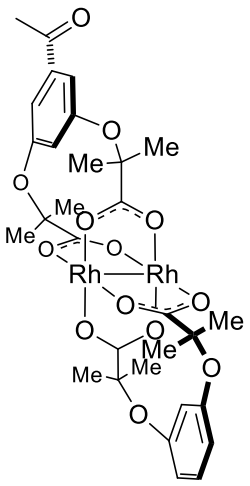
^{1}H-NMR (400 MHz, CD_2Cl_2) δ: 7.11 (t, *J* = 8.2 Hz, 2H), 6.52 (dd, *J* = 8.2, 2.1 Hz, 4H), 5.91 (t, *J* = 2.3 Hz, 2H), 1.39 (s, 24H). **^{13}C-NMR** (101 MHz, CD_2Cl_2) δ: 194.4, 156.4, 130.0, 115.2, 108.8, 81.2, 25.3. **HRMS** [M+Na$^+$] calc. for $C_{28}H_{32}NaO_{12}Rh_2$: 788.9923, found: 788.9896.



Dirhodium tetracarboxylate 3.6 was synthesized according to the synthesis protocol of Dirhodium tetracarboxylate **3.7**.

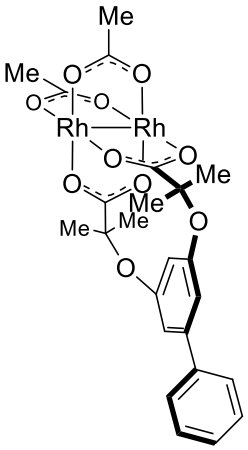
The chelate was synthesized by reacting 5 mg (7.71 μmol, 1 eq) dirhodium dicarboxylate **3.2** with three equivalent portions of diacid **3.10c** (3 mg, 7.71 μmol in total, 1 eq) in 0.4 mL 1,2-dichloroethane at 130°C in a closed micro wave vial for a total of 120 min. Upon cooling down the mixture to room temperature a green solid precipitated. The precipitate was collected and subsequently purified by preparative HPLC (MeCN / 0.1% TFA in H_2O, 2% to 80% over 28 min. t_R = 26 min, 254 nm) to give 1.5 mg (23%, 1.77 μmol) **3.6** as pale blue solid. 1.9 mg of unreacted dirhodium dicarboxylate **3.2** (t_R = 20 min) were reisolated.

^{1}H-NMR (600 MHz, 5% v/v MeOD in CD_2Cl_2) δ 7.17 (d, *J* = 2.3 Hz, 2H), 7.07 (d, *J* = 2.2 Hz, 2H), 6.15 (t, *J* = 2.3 Hz, 1H), 6.12 (t, *J* = 2.2 Hz, 1H), 2.50 (s, 3H), 1.37 (s, 12H), 1.37 (s, 12H). **^{13}C NMR** (151 MHz, 5% v/v MeOD in CD_2Cl_2) δ 197.7, 193.6, 193.5, 167.8, 156.6, 156.4, 139.3, 132.1, 116.8, 115.0, 113.8, 113.3, 81.4, 81.4, 30.3, 27.1, 25.2, 25.2. **HRMS** [M+Na$^+$] calc. for $C_{31}H_{34}NaO_{15}Rh_2$: 874.9922, found: 874.9900.



Dirhodium tetracarboxylate 3.7: According to a slightly modified procedure described by Du Bois.[176] A 4 mL microwave vial equipped with a stirring bar was charged with 72 mg (0.12 mmol, 1 eq) dirhodium chelate **3.1** and dissolved in 1.5 mL 1,2-dichloroethane. To this solution was added 16 mg (49 μmol, 0.34 eq) diacid **3.10c** and the vial was sealed with the corresponding cap and heated to 130°C in an oil bath. After 35 min the vial was removed from the oil bath and cooled to room temperature in a water bath. Another 14 mg (43 μmol, 0.32 eq) portion of diacid **3.10c** was added before resealing the vial. The mixture was heated to 130°C for another 35 min cooled to room temperature and charged with the third portion of 15 mg (46 μmol, 0.33 eq) diacid **3.10c**, sealed and heating was resumed at 130°C for 35 min. After cooling down the mixture to room temperature the solvent was evaporated under reduced pressure to give a dark green solid which was purified by manual flash chromatography (cyclohexane/EtOAc 4:1 to 2:3). A light green solid was isolated (76 mg) which was purified again by flash chromatography (cyclohexane/EtOAc 9:1 to 1:1). Three green bands were isolated where the second one was identified as the desired product **3.7**. 39 mg (41%, 48 μmol) of a green solid was obtained.

^{1}H NMR (400 MHz, DMSO) δ 7.10 (t, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 2.2 Hz, 2H), 6.49 (dd, *J* = 8.1, 2.3 Hz, 2H), 6.03 (t, *J* = 2.2 Hz, 1H), 5.83 (t, *J* = 2.3 Hz, 1H), 2.51 (s, 3H), 1.31 (s, 12H), 1.28 (s, 12H). **^{13}C NMR** (101 MHz, DMSO) δ 197.2, 193.1, 192.6, 155.6, 155.4, 138.6, 129.4, 114.8, 114.4, 112.5, 108.5, 80.6, 80.1, 26.9, 24.5, 24.4. **HRMS** [M+Na^{+}] calc. for $C_{30}H_{34}NaO_{13}Rh_2$: 831.0024, found: 831.0002.

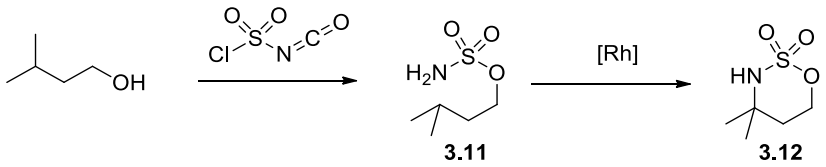


Rh complex 3.22: A dry round bottom flask under a N_2 atmosphere was charged with 9 mg (13.2 μmol, 1 eq) bromo complex **3.3**, 4.8 mg (39.5 μmol, 3 eq) phenyl boronic acid, 13 mg (39.5 μmol, 3 eq) Cs_2CO_3 and 3 mg (2.64 μmol, 0.2 eq) $Pd(PPh_3)_4$ and then immersed into a preheated oil bath at 50°C. After 1 h of stirring an aliquot and subsequent UPLC-MS analysis revealed the formation of the desired product. Same amounts were observed after 2 and 3 h according to UPLC-MS. During the reaction, the formation of black precipitate was observed, indicating formation of palladium black. Thus, another 1.5 mg (1.32 μmol, 1 eq) $Pd(PPh_3)_4$ was added and the reaction stirred for another 2 h at 50°C. Then, all volatiles were removed under reduced pressure, the residue dissolved in DMSO and injected into the preparative HPLC (MeCN / 0.1% TFA in H_2O, 2-80% over 25 min, t_R = 27 min, 254 nm), giving 3 mg (33%, 4.35 μmol) **3.22** as green solid.

^{1}H NMR (400 MHz, 5 % v/v MeOD in CD_2Cl_2) δ 7.53 – 7.49 (m, 2H), 7.43 – 7.38 (m, 2H), 7.36 – 7.31 (m, 1H), 6.76 (d, *J* = 2.2 Hz, 2H), 6.00 (t, *J* = 2.2 Hz, 1H), 1.89 (s, 6H), 1.40 (s, 12H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 193.32, 191.98, 156.73, 143.21, 140.85, 129.28, 128.14, 127.46, 114.07, 108.20, 81.17, 25.30, 23.73. **HRMS** $[M + Na]^+$: calc. for $C_{24}H_{26}NaO_{10}Rh_2$: 702.9528, found: 702.9521.

5.4.3 Synthesis of sulfamate ester 3.11 and nitrene insertion

Synthesis of sulfamate ester (**3.11**) was performed as described in the general procedure by Fruit.[177] Spectroscopical data was in agreement with previously reported data by Dillon.[178]



The nitrene insertion was performed according to and compared with the results of Brodsky[179] by Pascal Schmidt: crystalline white solid in 98% yield (105 mg, 0.636 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70-4.65 (m, 2H), 4.15 (s br, 1H), 1.80-1.72 (m, 2H), 1.42 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 69.3, 56.56, 35.61, 28.36.

For the comparison of catalysts and the additive scope, following **stock solutions (SS)** were made:

Sulfamate **3.11**: 8.35 mg (0.05 mmol) / 250 μL CD_2Cl_2
Cat **3.5**: 0.77 mg (1 μmol, 2 mol%) / 250 μL CD_2Cl_2
Cat **3.6**: 0.85 mg (1 μmol, 2 mol%) / 250 μL CD_2Cl_2
Cat **3.7**: 0.81 mg (1 μmol, 2 mol%) / 250 μL CD_2Cl_2 plus a drop of MeOD to help the catalyst dissolve

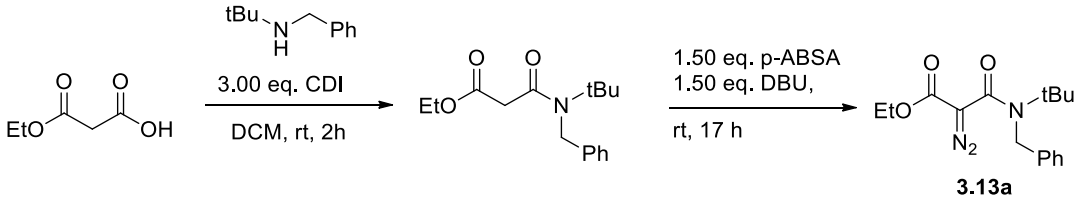
Reaction setup:

4.63 mg (0.12 mmol, 2.3 eq) MgO and 17.69 mg (0.055 mmol, 1.1 eq) $PhI(OAc)_2$ were weighed into a NMR tube, then first 0.25 mL of sulfamate **3.11** SS was added, then the additive (0.05 mmol, 1.00 eq.), followed by 0.25 mL Cat SS. Time was taken after catalyst addition and the tube was shaken on a Vortex Genie2. Time points indicate when the sample was removed from the shaker for measurement. Time was not stopped for measurement. Total time includes time used for previous measurements and shaking while not measuring.

Rh-cat	10 min	20 min	25 min	45 min	1 h	1.5 h	2 h	2.5 h	3 h	4 h
5	47 %	67 %		83 %	89 %	93 %	**95 %**			
6	65 %			82.6 %	85.5 %	88.5 %		93 %	94 %	**95 %**
7	78 %		86 %	93 %	**95 %**					
3.7 + MeOH	71 %				89 %	93 %	95 %			
3.7 + AcOH	60 %					84 %	86.2 %			**94 %**
3.7 + NEt_3	0 %				0 %					4 %

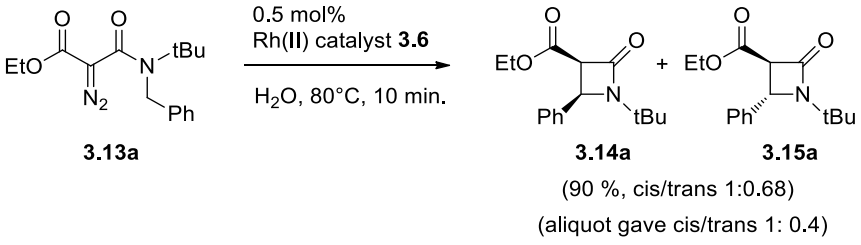
5.4.4 Synthesis of α-diazoacetamide 3.13a and carbene insertion

The first step was synthesized according to Qi.[180] The second step according to Choi[181]



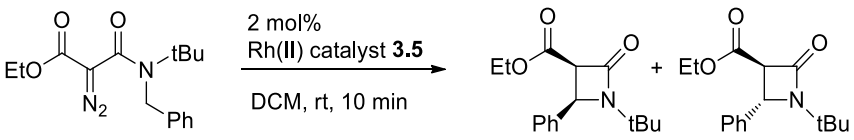
The catalytic transformation in DCM and H_2O was performed according to the general procedure of Candeias.[107]

Preparative reaction in H_2O:



To a suspension of 21.5 mg (70.6 µmol, 1 eq) diazo **3.13a** in 671 µL H_2O a stock solution of cat **3.6** (71.7 µL, 4.93 mM in H_2O / 500 mM Mes: pH=7.6, few drops 1M NaOH for solubility, 0.5 mol%) was added and the reaction mixture was stirred at 80°C for 10 min. Analysis of the mixture via ^{1}H-NMR spectroscopy after 10 min showed full conversion of the starting material to the target C-H insertion products. The obtained white solid was filtered off and washed with H_2O to yield 17.6 mg (91%, 63.9 µmol) β-lactams **3.14a** and **3.15a** as white solid. (This synthesis was performed by Stefanie Geigle)

Preparative reaction in DCM:



3.13a **3.14a** **3.15a**

(76 %, cis/trans 1: 0.29)

(aliquot after 10 min gave cis/trans 1: 0)

To a solution of 20.8 mg (68.3 µmol, 1 eq) diazo **3.13a** in 405 µL DCM a stock solution of cat **3.5** (278.8 µL, 4.91 mM in CH_2Cl_2, 2 mol %) was added and the reaction mixture was stirred at room temperature. Analysis of the mixture via ^{1}H-NMR spectroscopy after 10 min showed full conversion of the starting material to the single *cis* β-lactams **3.14a**. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (10 g C_{18} reverse phase silica, MeCN / 0.1% TFA in H_2O). The corresponding fractions were combined, the solvent removed under reduced pressure to obtain 14.3 mg (76%, 51.7 µmol) β-lactams **3.14a** and **3.15a** as white solid. (This synthesis was performed by Stefanie Geigle)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.27 (m, 10H, **3.14a, 3.15a**), 4.90 (d, *J* = 6.3 Hz, 1H, **3.14a**), 4.84 (d, *J* = 2.2 Hz, 1H, **3.15a**), 4.23 (dq, *J* = 7.2 Hz, 2H, **3.15a**), 4.21 (d, *J* = 6.2 Hz, 1H, **3.14a**), 3.76 (q, *J* = 7.1 Hz, 2H, **3.14a**), 3.69 (d, *J* = 2.2 Hz, 1H, **3.15a**), 1.31 (s, 9H, **3.14a**), 1.29 (t, 3H, **3.15a**), 1.26 (s, 3H, **3.15a**), 0.84 (t, *J* = 7.1 Hz, 3H**, 3.14a).**

^{13}C NMR (101 MHz, CD_2Cl_2) δ 166.6, 163.3, 137.6, 129.1, 128.8, 127.8, 61.3, 59.6, 57.0, 55.3 28.3.

For the **comparison of catalysts** and the additive scope in DCM, following **stock solutions (SS)** were made:

Cat **3.5**: 0.77 mg (1 µmol, 2 mol%) / 250 µL CD_2Cl_2
Cat **3.6**: 0.85 mg (1 µmol, 2 mol%) / 250 µL CD_2Cl_2
Cat **3.7**: 0.81 mg (1 µmol, 2 mol%) / 250 µL CD_2Cl_2 plus a drop of MeOD to help the catalyst dissolve

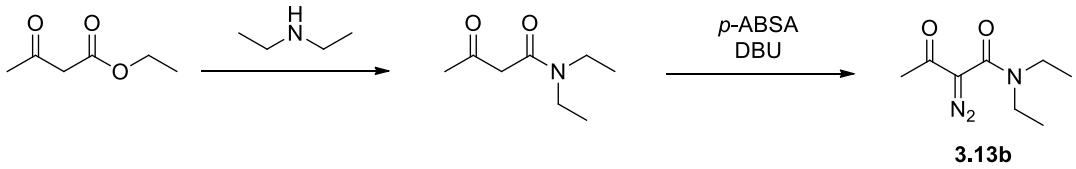
Reaction setup:

15.17 mg (0.05 mmol, 1 eq) Diazo **3.13a** was weighed into a NMR tube, then first 0.25 mL DCM, was added, then the additive (0.05 mmol, 1.00 eq.), followed by 0.25 mL Cat SS. Time was taken after catalyst addition and the tube was shaken on a Vortex Genie2. Time points indicate when the sample was removed from the shaker for measurement. Time was not stopped for measurement. Total time includes time used for previous measurements and shaking while not measuring.

Entry	Rh-cat	10 min	20 min	0.5 h	1 h	1.5 h	2 h	2.5 h	4.5 h
1	$Rh_2(OAc)_4$	**3.14a**: 8% **3.15a**: 0.4%				**3.14a**:69% **3.15a**: 3%			**3.14a: 94 %** **3.15a: 4.7%**
2	**3.5**	92 %	**98 %**						
3	**3.5**+ MeOH	79 %	91 %	**98 %**					
4	**3.5**+ AcOH	40 %		68 %		91 %	95 %	**97 %**	
5	**3.5**+ NEt_3								20 h = 0%
6	**3.6**	40 %		61 %	87 %	94 %	**98 %**		
7	**3.7**	71 %			**99 %**				

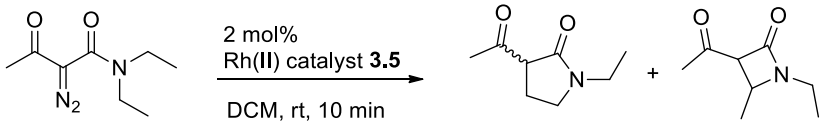
5.4.5 Synthesis of α-diazoacetamide 3.13b and carbene insertion

The first step was synthesized according to Huizenga[182]. The second step according to Koert[183]



3.13b

Preparative reaction in DCM:



3.13b **3.14b** 9:1 **3.15b**

To a solution of 43.3 mg (236 µmol, 1 eq) diazo **3.13b** in DCM (1.18 mL), a stock solution of Cat **3.5** (1.18 mL, 4 mM in DCM, 2 mol %) was added and the reaction mixture was stirred at room temperature. Analysis of the mixture via ^{1}H-NMR spectroscopy after 10 min showed full conversion of the starting material to the C-H insertion products in a ratio of 9:1 (**3.14b**:**3.15b**). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (10 g SiO_2, EtOAc/cHex 3:1) to obtain 5.2 mg (14%, 33.5 µmol) γ-lactam **3.14b** and 24.1 mg (66%, 155 µmol) β-lactam **3.15b** as colorless oils. (This synthesis was performed by Stefanie Geigle)

3.14b:

^{1}H NMR (250 MHz, $CDCl_3$) δ 3.54 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.42 – 3.30 (m, 2H), 3.27 (q, *J* = 7.3 Hz, 2H), 2.49 (ddt, *J* = 12.8, 8.5, 5.7 Hz, 1H), 2.38 (s, 3H), 1.99 (ddt, *J* = 13.1, 8.9, 5.5 Hz, 1H), 1.07 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 204.00, 169.35, 55.99, 44.87, 37.66, 30.05, 19.59, 12.44.

3.15b:

^{1}H NMR (250 MHz, $CDCl_3$) δ 4.08 (dq, *J* = 6.3, 2.1 Hz, 1H), 3.71 (d, *J* = 2.1 Hz, 1H), 3.43-3.27 (m, 1H), 3.07 (ddt, *J* = 14.6, 7.4, 6.6 Hz, 1H), 2.30 (s, 3H), 1.34 (d, *J* = 6.2 Hz, 3H), 1.17 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 200.80, 162.40, 69.51, 48.56, 35.38, 29.97, 17.82, 13.34.

For the **comparison of catalysts**, following **stock solutions (SS)** were made:

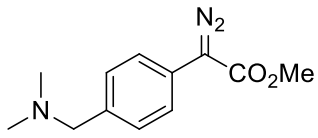
Diazo **3.13b**: 9.2 mg (0.05 mmol) / 250 μL CD_2Cl_2
Cat **3.5**: 0.77 mg (1 μmol, 2mol%) / 250 μL CD_2Cl_2
Cat **3.6**: 0.85 mg (1 μmol, 2mol%) / 250 μL CD_2Cl_2
Cat **3.7**: 0.81 mg (1 μmol, 2mol%) / 250 μL CD_2Cl_2 plus a drop of MeOD to help the catalyst dissolve

Reaction setup:

0.25 mL diazo **3.13b** SS was put into a NMR tube, then 0.25 mL Cat SS. Time was taken after catalyst addition and the tube was shaken on a Vortex Genie2. Time was taken after catalyst addition and the tube was shaken on a Vortex Genie2. Time points indicate when the sample was removed from the shaker for measurement. Time was not stopped for measurement. Total time includes time used for previous measurements and shaking while not measuring.

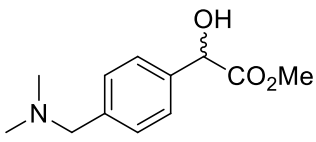
Entry	Rh-cat	10 min	20 min	1 h
1	**3.5**	**3.14b** = 88 % **3.15b** = 9.6 %		
2	**3.6**	**3.14b** = 53 % **3.15b** = 7.4 %	**3.14b** = 66 % **3.15b** = 8.6 %	**3.14b** = 85 % **3.15b** = 11 %
3	**3.7**	**3.14b** = 86 % **3.15b** = 10.3 %		

5.4.6 Synthesis of α-diazo methylester 3.16 and O-H insertion in water



3.16

The synthesis and spectroscopic characterization of α-diazo methylester **3.16**, as well as its catalytic decomposition to **3.17** has been described by Gillingham and co-workers.[94]



Preparative synthesis of **3.17**: A stock solution of **3.16** (125 mM in MES pH 6, ca. 0.7 mL) was treated with 4 mg (89.0 μmol, 10 mol%) $Rh_2(OAc)_4$ and the mixture stirred under ambient conditions. The progress of the reaction was monitored by UPLC-MS (254 nm) and after stirring for two days the creamy pink

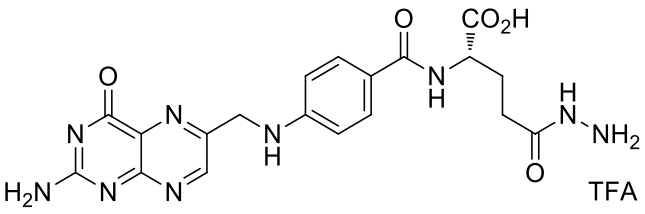
solution was lyophilized. The greyish solid was dissolved in DCM and the precipitate (MES) was filtered off through a plug of cotton followed by removal of the solvent under reduced pressure. The crude sample was purified by flash chromatography on a Biotage Isolera Four device (20% MeOH in DCM). The product eluted after two column volumes and the purity of the fractions was analyzed by TLC (20% MeOH in DCM, $KMnO_4$). The pure fractions were combined and concentrated under reduced pressure to give 8.4 mg (43%, 37.6 μmol) **3.17** as colorless oil which crystallized upon standing.

R_f = 0.26 (20% MeOH in DCM). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.39-7.35 (m, 2H), 7.33-7.29 (m, 2H), 5.17 (s, 1H), 3.76 (s, 3H), 3.43 (s, 2H), 2.23 (s, 6H). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 174.25, 138.72, 137.42, 129.64, 126.74, 72.86, 63.85, 53.16, 45.22. **HRMS** [$M+H^+$] calc. for $C_{12}H_{18}NO_3$: 224.1287, found: 224.1284.

This synthesis, characterization and analyses were performed by Pascal Schmidt.

5.4.7 Synthesis of hydrazides

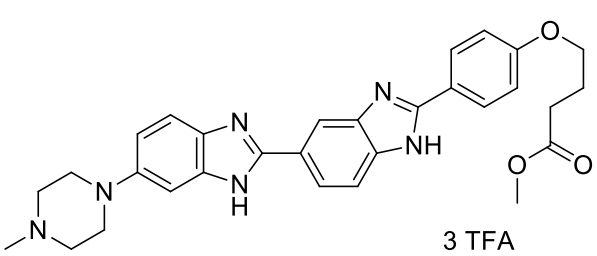
Biotin hydrazide (**3.18a**) and maleimidpropionic acid hydrazide TFA salt (BMPH) (**3.20a**) were purchased from Pierce (Prod. Nr. 21339 & 22297). Folic acid hydrazide and Hoechst hydrazide were synthesized as followed:



Folic hydrazide 3.19a: According to Guo[119] with minor modifications: 200 mg (0.45 mmol, 1 eq) folic acid was dissolved in a dry round bottom flask with 20 mL of dry DMSO under a N_2 atmosphere and the flask was then wrapped in aluminum foil. Then, 103 mg (0.50 mmol, 1.1 eq) DCC and 57 mg (0.50 mmol, 1.1 eq) *N*-Hydroxysuccinimide were added and the solution was stirred for 16 h at room temperature. The obtained slurry was subsequently filtered through a sintered glass frit and the filtrate was added dropwise to 0.32 mL (6.57 mmol, 14.5 eq) stirring NH_2NH_2-hydrate at room temperature. After 30 min, 4 mL of aqueous 0.5 N HCl was added dropwise (heat formation). The resulting solution was transferred into a 50 mL Falcon tube. 15 mL MeCN and 15 mL ether were added to precipitate the products. After centrifugation and decantation of the supernatant, the yellow pellet was suspended in 20 mL of EtOH and 5 mL of Et_2O, centrifuged and decanted. The procedure was repeated with 25 mL of EtOH, then (for the convenience of drying) with 25 mL of Et_2O. 170 mg of a crude yellow solid were obtained, which were subsequently dissolved in water and purified by preparative HPLC (MeCN

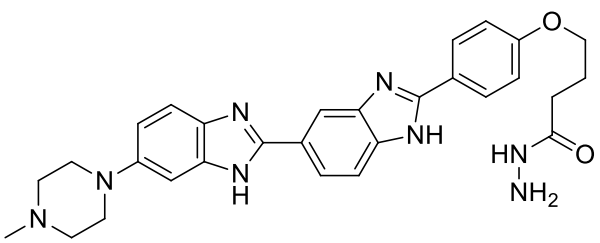
/ 0.1% TFA in H_2O, 2% to 10% over 25 min, t_R = 21 min, 280 nm). 4 fractions were collected, the desired FA-γ-hydrazide (**3.19a**) eluted as the second band. After lyophilization 45 mg (17.5%, 0.079 mmol) FA-γ-hydrazide (**3.19a**) was obtained as the corresponding TFA salt as fluffy yellow solid.

^{1}H NMR (500 MHz, DMSO) δ 10.61 (s, 1H), 8.65 (s, 1H), 8.21 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 6.64 (d, *J* = 8.9 Hz, 2H), 4.49 (s, 2H), 4.34 (ddd, *J* = 10.0, 7.9, 4.7 Hz, 1H), 2.31 (t, *J* = 7.5 Hz, 2H), 2.16 – 2.07 (m, 1H), 1.95 – 1.89 (m, 1H). **^{13}C NMR** (151 MHz, DMSO) δ 173.7, 171.1, 166.4, 160.9, 155.5, 153.7, 150.8, 148.9, 148.5, 129.1, 128.0, 121.3, 111.2, 51.7, 45.9, 29.5, 26.0. **HRMS** [M+H$^+$] calc. for $C_{19}H_{22}N_9O_5$: 456.1738, found: 456.1736.



Hoechst methyl ester 3.21aa: Addapted from Rastogi[184]: A dry round bottom flask under a N_2 atmosphere was charged with 50 mg (94 μmol, 1 eq) Hoechst 33258 and was dissolved in 1 mL of dry DMF. Then 65 mg (468 μmol, 5 eq) K_2CO_3 and 18 μL (140 μmol, 1.5 eq) methyl-4 bromobutyrate was added. The slurry was subsequently immersed into a pre-heated oil bath at 60°C and was stirred for 14 h. After cooling to room temperature, the mixture was filtered through a sintered glass frit and the solid was rinsed once with 1 mL of DMF. The combined filtrate (DMF solution) was then injected into the preparative HPLC (MeCN / 0.1% TFA in H_2O, 2% to 30% over 25 min, t_R = 25 min, 254 nm) and product **3.21aa** was eluted as a yellow solution. After lyophilization, 41 mg (51%, 47 μmol) of **3.21aa** was obtained as yellow fluffy solid (TFA salt).

^{1}H NMR (400 MHz, MeOD) δ 8.08 (d, *J* = 1.5 Hz, 1H), 7.88 (d, *J* = 8.9 Hz, 2H), 7.84 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.57 (d, *J* = 9.0 Hz, 1H), 7.26 (dd, *J* = 9.1, 2.2 Hz, 1H), 7.17 (d, *J* = 2.1 Hz, 1H), 6.94 (d, *J* = 8.9 Hz, 2H), 3.93 (t, *J* = 6.3 Hz, 2H), 3.88 (s br, 2H), 3.70 (s, 3H), 3.65 (s br, 2H), 3.31 (s br, 2H), 3.17 (s br, 2H), 3.01 (s, 3H), 2.50 (t, *J* = 7.3 Hz, 2H). **^{13}C NMR** (101 MHz, MeOD) δ 175.3, 163.5, 163.1, 162.8, 155.2, 150.4, 150.0, 140.4, 138.2, 134.6, 130.2, 128.2, 123.8, 119.3 (1:1:1 t, *J* = 18.5 Hz), 116.5, 116.3, 115.5, 114.9, 100.9, 68.4, 54.6, 52.2, 43.6, 31.2, 25.6. (One signal missing, 1:1:1 signal is assumed to be due to deuteration with CD_3OD). **HRMS** [M+H$^+$] calc. for $C_{30}H_{32}N_6O_3$: 525.2609, found: 525.2602.

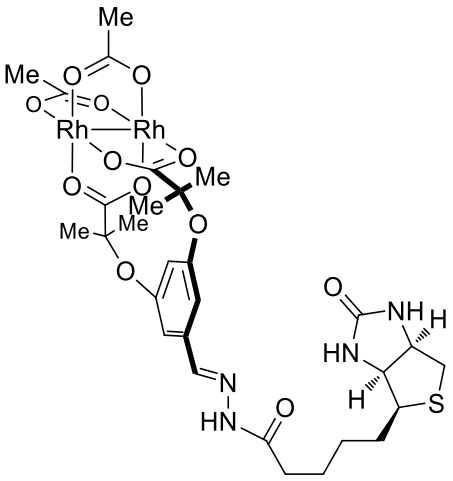


Hoechst hydrazide **3.21a**: 29 mg (0.033 mmol, 1 eq) Hoechst methyl ester **3.21aa** was dissolved in 0.5 mL of EtOH in a N_2 purged heart shaped flask. While stirring at room temperature, 1 mL (21 mmol, 614 eq) NH_2NH_2-hydrate was added. The yellow solution turned immediately to almost colorless and was then heated with an oil bath to 60°C. It was stirred for 1.5 h and a suspension resulted. After letting the mixture cool down to room temperature, it was transferred into a 20 mL Falcon tube, diluted with 5 mL of additional EtOH and subsequently centrifuged. The supernatant was removed and 10 mL of Et_2O was added. After shaking, the suspension was centrifuged again, the supernatant was discarded and 14 mg (80%, 0.026 mmol) **3.21a** was obtained as beige solid.

^{1}H NMR (400 MHz, 10 % v/v DMSO-d_6 in MeOD) δ 8.28 (s, 1H), 8.07 (d, *J* = 8.8 Hz, 2H), 7.97 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.15 (d, *J* = 1.8 Hz, 1H), 7.10 (d, *J* = 8.9 Hz, 2H), 7.06 (dd, *J* = 8.8, 2.2 Hz, 1H), 4.09 (t, *J* = 6.2 Hz, 2H), 3.29 – 3.22 (m, 4H), 2.81 – 2.72 (m, 4H), 2.38 (t, *J* = 7.4 Hz, 2H), 2.17 – 2.06 (m, 2H). **^{13}C NMR** (101 MHz, 10 % v/v DMSO-d_6 in MeOD) δ 174.36, 164.57*, 162.04*, 162.38, 160.54*, 155.21, 153.65, 149.45, 129.64, 128.89 (1:1:1 t, *J* = 24.3 Hz), 125.65, 123.03, 122.49, 116.29, 116.15, 68.39, 56.00, 51.36, 45.84, 31.43, 26.38. (4 Signals missing; not observable in 13C and high resolution HMBC spectra. *Only visible in high resolution HMBC. 1:1:1 signal is assumed to be due to deuteration with CD_3OD). **HRMS** [M+H$^+$] calc. for $C_{29}H_{33}N_8O_2$: 525.2721, found: 525.2716.

5.4.8 General procedure for Aldehyde-Hydrazide conjugation reactions

A dry, heart shaped flask under a N_2 atmosphere was charged with 4 mg (6.33 μmol, 1 eq) Rh-Aldehyde **3.4** and was subsequently dissolved in 0.4 mL DMSO-d_6. Then, hydrazide **3.18a-3.21a** (1 eq, 6.33 μmol) was added followed by additional TFA in case needed (see below). The red brownish solution was stirred at room temperature for the indicated time below. Reaction control was done by ^{1}H NMR aliquots. The reaction solution was then diluted with 0.6 mL of DMSO and injected into the preparative HPLC. The product bands were collected and lyophilized. The products **3.18b-3.21b** were obtained as a mixture of s-*cis*/s-*trans* isomers due to restricted rotation of the C-N bond in the hydrazone.[120] NMR signals which are not distinguishable and thus occur in the s-*cis* and s-*trans* product are marked with an asterisk (*). The assignment was done with high resolution HMBC and HMQC spectra.



3.18b
Reaction time: 2.5 h.
Additive: 1 eq TFA (0.5 μL)
Elution: MeCN / H_2O, 2% to 60% over 30 min. t_R = 27 min
Appearance: light purple solid, 4 mg, 70% yield.

s-*cis* isomer:
^{1}H-NMR (600 MHz, DMSO-d6) δ: 11.35 (s, 1H), 7.99 (s, 1H), 6.80 (d, *J* = 2.1 Hz, 2H), 6.44 (s br, 1H)*, 6.36 (d, *J* = 9.1 Hz, 1H)*, 5.74 (t, *J* = 2.0 Hz, 1H), 4.33 – 4.26 (m, 1H)*, 4.14 (s br, 1H)*, 3.12 (s br, 1H)*, 2.87 – 2.78 (m, 1H)*, 2.64 – 2.54 (m, 1H)*, 2.19 (t, *J* = 7.2 Hz, 2H), 1.81 (s, 6H)*, 1.69 – 1.61 (m,1H)*, 1.61 – 1.55 (m, 2H)*, 1.53 – 1.45 (m, 1H)*, 11.43 – 1.33 (m, 2H)*, 1.31 (s, 12H)*.

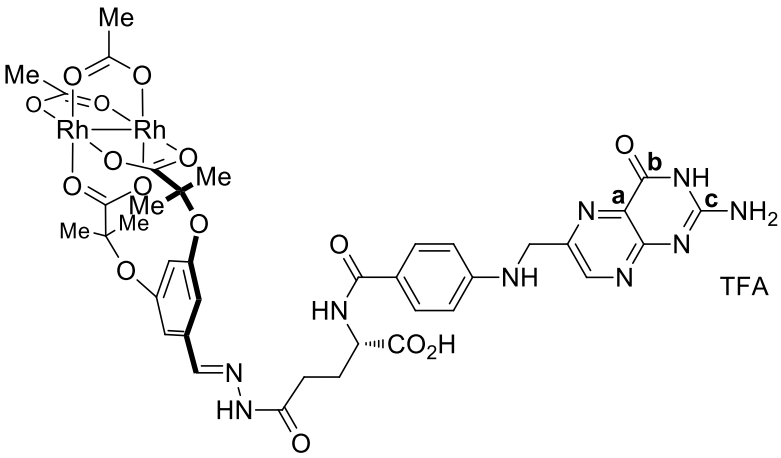
^{13}C-NMR (151 MHz, DMSO-d_6) δ: 192.78*, 192.0*, 169.16, 163.23*, 156.05*, 145.23, 136.62, 113.01, 109.45, 80.80*, 61.57*, 59.61*, 55.94*, 40.35*, 34.52, 28.79*, 28.81*, 25.51, 25.12*, 24.06*.

s-*trans* isomer:
^{1}H-NMR (600 MHz, DMSO-d_6) δ: 11.21 (s, 1H),7.81 (s, 1H), 6.75 (s br, 2H), 6.44 (s br, 1H)*, 6.36 (d, *J* = 9.1 Hz, 1H)*, 5.72 (s br, 1H), 4.33 – 4.26 (m, 1H)*, 4.14 (s br, 1H)*, 3.12 (s br, 1H)*, 2.87 – 2.78 (m, 1H)*, 2.64 –2.54 (m, 1H)*, 2.59 (t, *J* = 7.8 Hz, 2H), 1.81 (s, 6H)*, 1.69 – 1.61 (m,1H)*, 1.61 – 1.55 (m, 2H)*, 1.53 – 1.45 (m, 1H)*, 1.43 – 1.33 (m, 2H)*, 1.31 (s, 12H)*.

^{13}C-NMR (151 MHz, DMSO-d6) δ: 192.78*, 192.0*, 174.74, 163.23*, 156.05*, 141.94, 136.0, 112.53, 109.15, 80.80*, 61.57*, 59.61*, 55.94*, 40.35*, 32.23, 28.79*, 28.81*, 24.76, 25.12*, 24.06*.

HRMS $[M + Na]^+$: calc. for $C_{29}H_{38}N_4NaO_{12}Rh_2S$: 895.0209, found: 895.0206.

3.19b
Reaction time: 3 h.
Additive: none
Elution: MeCN / 0.1% TFA in H_2O, 2% to 60% over 28 min. t_R = 20 min
Appearance: orange solid, 4 mg, 51% (90% pure due to product instability).



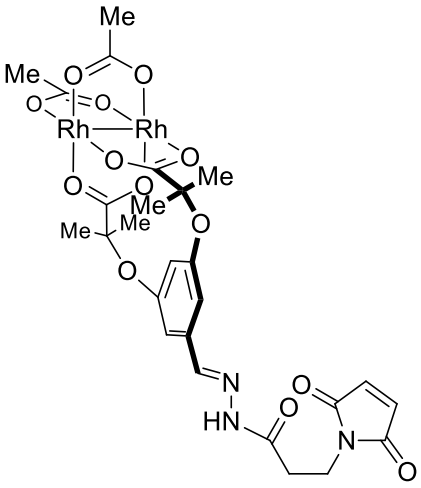
s-*cis* isomer:
^{1}H-NMR (500 MHz, DMSO-d_6) δ: 11.39 (s, 1H), 8.65 (s, 1H), 7.95 (s, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 2.1 Hz, 2H), 6.65 (d, *J* = 8.8 Hz, 2H), 5.74 (t, *J* = 2.2 Hz, 1H), 4.49 (s, 2H), 4.35 – 4.30 (m, 1H), 2.31 (t, *J* = 7.8 Hz, 2H), 2.19 – 2.09 (m, 1H)*, 2.03 – 1.92 (m, 1H)*, 1.80 (s, 12H), 1.31 (s, 6H).

^{13}C-NMR (126 MHz, DMSO-d6) δ: 192.6*, 191.9*, 174.0*, 168.4, 166.6*, 156.7*, 155.8*, 151.0*, 150.9*, 148.4*, 144.6, 136.3, 128.7*, 121.5*, 112.3, 110.9*, 108.7, 80.5*, 51.8*, 45.6*, 30.6, 25.5*, 24.5*, 23.2*. Carbon signals for a, b and c (*vide supra*) were not observable in the HMBC spectrum.

s-*trans* isomer:
^{1}H-NMR (500 MHz, DMSO-d_6) δ: 11.29 (s, 1H), 8.63 (s, 1H), 7.79 (s, 1H), 7.64 (d, *J* =8.8 Hz, 2H), 6.73 (d, *J* = 2.2 Hz, 2H), 6.62 (d, *J* = 8.8 Hz, 2H), 5.72 (t, *J* = 2.2 Hz, 1H), 6.46 (s, 2H), 4.40 – 4.35 (m, 1H), 2.77 – 2.68 (m, 2H), 2.19 – 2.09 (m, 1H)*, 2.03 – 1.92 (m, 1H)*, 1.81 (s, 12H), 1.28 (s, 6H).

^{13}C-NMR (126 MHz, DMSO-d_6) δ: 192.6*, 191.9*, 174.0*, 174.3, 166.6*, 156.7*, 155.8*, 151.0*, 150.9*, 148.4*, 141.5, 136.2, 128.7*, 121.5*, 111.9, 110.9*, 108.6, 80.5*, 51.8*, 45.6*, 28.5, 25.5*, 24.5*, 23.2*. Carbon signals for a, b and c (*vide supra*) were not observable in the HMBC spectrum.

HRMS [M + Na^+] calc. for $C_{38}H_{41}N_9NaO_{15}Rh_2$: 1092.0724, found: 1092.0740.



3.20b
Reaction time: 3 h.
Additive: none
Elution: MeCN / H_2O, 2% to 70% over 28 min. t_R = 23 min
Appearance: light green solid, 3.3 mg, 65% yield.

s-*cis* isomer:
^{1}H-NMR (600 MHz, DMSO-d_6) δ: 11.48 (s, 1H), 7.97 (s, 1H), 7.03 (s, 2H), 6.80 (d, *J* = 2.1 Hz, 2H), 5.75 (t, *J* = 2.1 Hz, 1H), 3.68 (t, *J* = 7.2 Hz, 2H), 2.49 (t, *J* = 7.2 Hz, 2H), 1.81 (s, 6H)*, 1.32 (s, 12H)*.

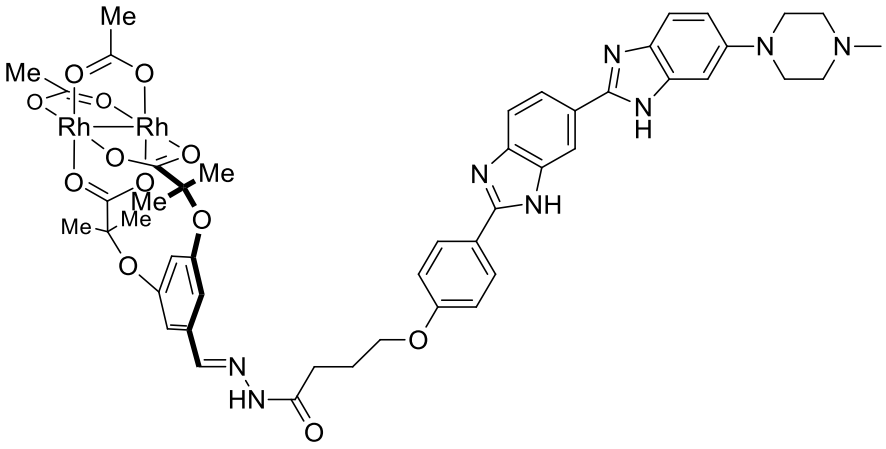
^{13}C-NMR (151 MHz, DMSO-d6) δ: 192.32, 191.69*, 170.76*, 165.98, 155.63*, 145.28, 136.02, 134.62, 112.62, 109.10, 80.28, 33.66, 32.81, 24.64*, 23.48*.

s-*trans* isomer:
^{1}H-NMR (600 MHz, DMSO-d_6) δ: 11.35 (s, 1H), 7.81 (s, 1H), 6.97 (s, 2H), 6.76 (d, *J* = 2.1 Hz, 2H), 5.73 (t, *J* = 2.1 Hz, 1H), 3.70 (t, *J* = 7.2 Hz, 2H), 2.86 (t, *J* = 7.2 Hz, 2H), 1.81 (s, 6H)*, 1.32 (s, 12H)*.

^{13}C-NMR (151 MHz, DMSO-d_6) δ: 192.36, 191.69*, 171.90, 170.76*, 155.63*, 142.29, 135.91, 134.54, 112.22, 108.86, 80.26, 33.67, 31.00, 24.64*, 23.48*.

HRMS [M + Na^+] calc. for $C_{26}H_{29}N_3NaO_{13}Rh_2$: 819.9703, found: 819.9697.

3.21b
Reaction time: 1 h.
Additive: 10 eq TFA (5 μL)
Elution: MeCN / H_2O, 2% to 80% over 28 min. t_R = 16 min
Appearance: green solid, 4 mg, 55% yield (containing minor grease impurities).



s-*cis* isomer:
^{1}H-NMR (600 MHz, DMSO-d_6) δ: 11.47 (s, 1H), 8.38 (s br, 1H)*, 8.17 (s, 1H)*, 8.17 (d, *J* = 17.1 Hz, 1H)*, 8.02 (d, *J* = 9.2 Hz, 1H)*, 8.01 (s, 1H), 7.79 (s br, 1H)*, 7.62 (d, *J* = 8.1 Hz, 1H)*, 7.17 (d, *J* = 8.5 Hz, 4H), 6.82 (d, *J* = 2.1 Hz, 2H), 5.75 (t, *J* = 2.0 Hz, 1H), 4.13 (t, *J* = 6.5 Hz, 2H), 3.93 – 3.80 (m, 2H)*, 3.62 – 3.53 (m, 2H)*, 3.27 – 3.16 (m, 2H)*, 3.08 – 2.97 (m, 2H)*, 2.90 (s, 3H)*, 2.42 (t, *J* = 7.3, 2H), 2.10 – 2.03 (m, 2H)*, 1.81 (s, 3H), 1.32 (s, 12H).

^{13}C-NMR (151 MHz, DMSO-d_6) δ: 191.99*, 191.27*, 168.30, 160.63, 155.38*, 144.73, 144.53, 121.64*, 115.50*, 115.48*, 112.34, 108.75, 79.82*, 66.97, 52.82*, 46.82*, 41.95*, 30.03, 24.48*, 24.22, 23.36*. Due to peak broadening, no signals were obtained for the carbons in the benzo-imidazole systems (2 x 7 carbons).

s-*cis* trans:
^{1}H-NMR (600 MHz, DMSO-d_6) δ: 11.32 (s, 1H), 8.38 (s br, 1H)*, 8.17 (s, 1H)*, 8.17 (d, *J* = 17.1 Hz, 1H)*, 8.02 (d, *J* = 9.2 Hz, 1H)*, 7.84 (s, 1H), 7.79 (s br, 1H)*, 7.62 (d, *J* = 8.1 Hz, 1H)*, 7.17 (d, *J* = 9.0 Hz, 4H), 6.79 (d, *J* = 2.1 Hz, 2H), 5.73 (t, *J* = 2.1 Hz, 1H), 4.16 (t, *J* = 6.4 Hz, 2H), 3.93 – 3.80 (m, 2H)*, 3.62 – 3.53 (m, 2H)*, 3.27 – 3.16 (m, 2H)*, 3.08 – 2.97 (m, 2H)*, 2.90 (s, 3H)*, 2.81 (t, *J* = 7.2, 2H), 2.10 – 2.03 (m, 2H)*, 1.80 (s, 3H), 1.31 (s, 12H).

^{13}C-NMR (151 MHz, DMSO-d_6) δ: 191.99*, 191.27*, 174.05, 160.74, 155.38*, 141.60, 141.53, 121.64*, 115.50*, 115.48*, 111.85, 108.47, 79.82*, 67.09, 52.82*, 46.82*, 41.95*, 28.26, 24.48*, 23.56, 23.36*. Due to peak broadening, no signals were obtained for the carbons in the benzo-imidazole systems (2 x 7 carbons).

HRMS [M + Na^+] calc. for $C_{48}H_{53}N_8O_{12}Rh_2$: 1139.1888, found: 1139.1887.

5.4.9 Biological evaluations

Cell culture

U-87 MG cells were grown in 75 cm^2 cell culture flasks (BD Bioscience) at 37°C under a 5% CO_2 atmosphere in the cell culture medium (normal cell grow conditions). When cells reached a confluency of about 80%, they were split in a 1 : 10 ratio. To prepare the cell culture medium 50 ml fetal bovine serum (BioConcept AG), 10 mL 10'000 U/mL penicillin and 10'000 µg/mL streptomycin (Gibco) were filled up to 500 mL with fresh Dulbecco's modified eagle's medium (DMEM) (Sigma). The medium was sterile filtered through a 0.2 µm vacuum filter (Millipore). The cells were subcultured by trypsinization.

Preparation for live cell imaging

For live images 50'000 U-87 cells were seeded into each 8-well microscope chamber slides (Nunc) for 24 h in normal cell culture conditions. Before adding the samples to the cells, medium was removed. Then, the cells were incubated with 40 µL of 100 µM **3.21b** dissolved in 1:1 Ethylene glycol: PBS for 30 min. Subsequently, cells were washed with PBS and wells were filled up with 400 µL PBS.

Cell imaging

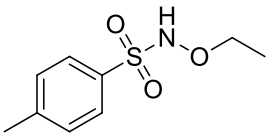
Cell imaging was performed by confocal laser scanning microscopy (CLSM) with a Zeiss 510-META/Confocor2 microscope equipped with a laser diode (405 nm) and a 40x water-immersion objective (Zeiss C-Apochromat 40x/1.2 W corr). The samples were excited at 405 nm and the emission was collected with a broad pass filter at 420-480 nm. The pinholes were set to 61 µm. The cells were imaged in multitrack mode with a resolution of 1024 x 1024 pixels (225 µm x 225 µm) with a pixel time of 12.6 µs, whereas every pixel is the mean of two measurements.

5.5 Hydroxylamine and *N*-(*t*-butoxy)carbamate synthesis

Important: Different results depending on the kind of K_2CO_3 were obtained. K_2CO_3 was purchased from Alfa Aesar, anhydrous, 99% (A16625) which comes in spherical grains. It was crucial to grind it into fine powder with the help of a mortar. The obtained hygroscopic powder was stored in a well-sealed vial and used for not more than 2 weeks.

α,α,α-Trifluorotoluene (TFT) was purchased from Sigma Aldrich in a sure/seal bottle and used as delivered.

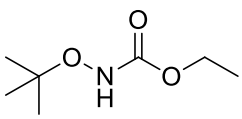
5.5.1 Syntheses of tosyl hydroxylamines not according to the general procedure



Hydroxylamine 4.2: 20 mg (0.12 mmol, 1 eq) of tosyl sulfonamide was added into a dry schlenk falsk under a N_2 atmosphere and suspended in 1 mL dry DCM. Then 11 mg (0.27 mmol, 2.3 eq) MgO, 42 mg (0.13 mmol, 1.1 eq) $PhI(OAc)_2$ and in the end 1.8 mg (2.3 μmol, 0.02 eq) of **3.5** were added in the given order. The suspension stirred at room temperature for 2 h and reaction control by ^{1}H NMR suggested 55% conversion of the tosyl sulfonamide. No more conversion was observed upon continued stirring. The mixture was purified by flash chromatography according to the general procedure. 4 mg (16%, 0.019 mmol) of **4.11** were obtained as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.13 (m, 2H), 7.11 – 7.05 (m, 2H), 6.42 (s, 1H), 4.26 (q, *J* = 7.14 Hz, 2H), 2.33 (s, 3H), 1.35 (t, *J* = 7.14 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.35, 133.65, 130.21, 120.82, 68.23, 20.96, 14.74. **HRMS** [M + Na^+] calc. for $C_9H_{13}NNaO_3S$: 238.0508 found: 238.0508.

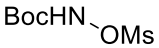
5.5.2 Synthesis of *N*-(*t*-butoxy)carbamates not according to the general procedure



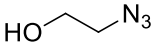
***N*-(*t*-butoxy)carbamate 4.11b**: A 5 mL dry Schlenk flask was charged with 1 mL dry DCM, 20 mg (0.07 mmol, 1 eq) of reagent **6a** and 30 mg (0.21 mmol, 3 eq) K_2CO_3 and then 14 μL (0.24 mmol, 3.5 eq) EtOH was added. In one case additional 0.6 mg (1.4 μmol, 0.02 eq) $Rh_2(OAc)_4$ was added. The slurry stirred at 40°C for 16 h overnight. After removal of all volatiles, ^{1}H NMR suggested pure product. Purified by flash chromatography according to the general procedure. (10% EtOAc in cyclohexane -> 25% EtOAc in cyclohexane, $KMnO_4$). Colorless oil, no yield is given due to volatility issues.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.25 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.50, 81.26, 61.81, 26.18, 14.47. **HRMS** [M + Na^+] calc. for $C_7H_{15}NNaO_3$: 184.0944 found: 184.0946.

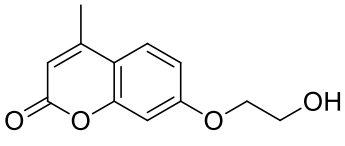
5.5.3 Synthesis of known compounds



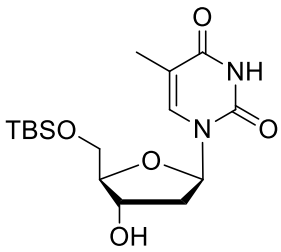
Compound **4.10b** was synthesized according to Masruri[185].



Compound **4.12c** was synthesized according to Hong using the procedure for 3-azido propanol (S1).[186]



Compound **4.12i** was synthesized according to Shaughnessy[187]. Because only 80% pure compound was obtained (1g scale) it was recrystallized from 40 mL (70°C) EtOAc in the freezer.



Compound **4.12k** was synthesized according to Temburnikar[188]

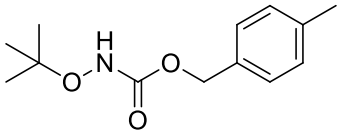
5.5.4 General Procedure for the synthesis of *N*-(*t*-butoxy)carbamates

An oven-dried 5 mL Schlenk flask under a N_2 atmosphere was charged with 2 mL of dry α,α,α-trifluorotoluene and a magnetic stir bar. Separately a stirred oil bath was preheated to 70°C. Then, 85 mg (0.4 mmol, 2 eq.) *N*-Boc *O*-mesyl hydroxylamine **4.10b** was added into the flask. To help to dissolve reagent **4.10b**, the flask was immersed into the preheated oil bath for ca. 30 sec. Once a clear solution resulted, the alcohol (0.2 mmol, 1 eq.) was added (with a Hamilton syringe in case of a liquid), followed by 56 mg (0.4 mmol, 2 eq.) ground K_2CO_3. The vigorously stirred suspension was immersed into the preheated oil bath and stirred for the indicated time (or over-night).

In case of hygroscopic substrates (sugars, amino acids,…) they were dissolved in benzene and concentrated in the Schlenk flask 3 times prior to the addition of α,α,α-trifluorotoluene and reagent/reactant.

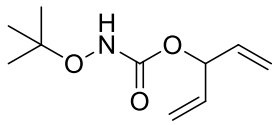
After ^{1}H NMR aliquots suggested full conversion of the alcohol (shift from around 3.5 ppm to 4.5 ppm) or the absence of reagent **4.10b**, the sample was allowed to cool to room temperature, the contents were transferred into a round bottom flask and all volatiles were subsequently removed under reduced pressure. The obtained solid was re-suspended in DCM and a spoon of silica was added. After again having removed all volatiles, the silica laiden product was dry-loaded on a self-packed 10 g Biotage column and eluted with the given gradient over 14 column volumes, collecting fractions of 12 mL.

5.5.5 Characterization of *N*-(*t*-butoxy)carbamates



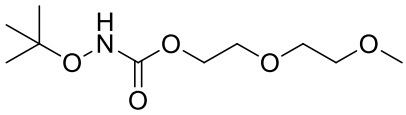
***N*-(*t*-butoxy)carbamate 4.13a** was synthesized in 20 h according to the general procedure and purified by flash chromatography (5% EtOAc in cyclohexane -> 15% EtOAc in cyclohexane, $KMnO_4$). 25 mg (53%) were obtained as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.24 (m, 2H), 7.18 – 7.14 (m, 2H), 6.99 (s, 1H), 5.12 (s, 2H), 2.35 (s, 3H), 1.24 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.42, 138.33, 132.89, 129.35, 128.58, 81.46, 67.50, 26.30, 21.32. **HRMS** [M + Na^+] calc. for $C_{13}H_{19}NNaO_3$: 260.1257 found: 260.1261.



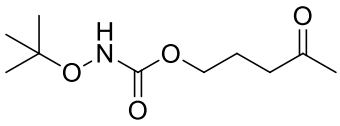
***N*-(*t*-butoxy)carbamate 4.13b** was synthesized in 48 h according to the general procedure and purified by flash chromatography (5% EtOAc in cyclohexane -> 15% EtOAc in cyclohexane, $KMnO_4$). 21 mg (53%) were obtained as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1H), 5.84 (ddd, *J* = 17.2, 10.4, 6.1 Hz, 2H), 5.65 (tt, *J* = 6.04, 1.23, 1H), 5.33 (dt, *J* = 17.2, 1.3 Hz, 2H), 5.24 (dt, *J* = 10.5, 1.2 Hz, 2H), 1.25 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.59, 135.03, 117.87, 81.48, 76.59, 26.33. **HRMS** [M + Na^+] calc. for $C_{10}H_{17}NNaO_3$: 222.1106 found: 222.1101.



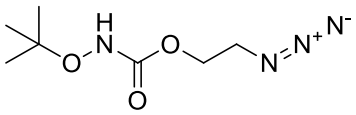
***N*-(*t*-butoxy)carbamate 4.13c** (diethylene glycol methyl ester was dried over anhydrous K_2CO_3 and distilled at 220°C at atm. pres. prior use) was synthesized in 3 h according to the general procedure and purified by flash chromatography (20% EtOAc in cyclohexane -> 50% EtOAc in cyclohexane, $KMnO_4$). 25 mg (53%) were obtained as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 1H), 4.29 (dd, *J* = 5.3, 4.2 Hz, 2H), 3.70 (dd, *J* = 5.3, 4.2 Hz, 2H), 3.63 (dd, *J* = 5.8, 3.2 Hz, 2H), 3.54 (dd, *J* = 6.2, 3.0 Hz, 2H), 3.38 (s, 3H), 1.24 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.31, 81.52, 71.99, 70.59, 69.47, 64.77, 59.21, 26.29. **HRMS** [M + Na^+] calc. for $C_{10}H_{21}NNaO_5$: 258.1317 found: 258.1312.



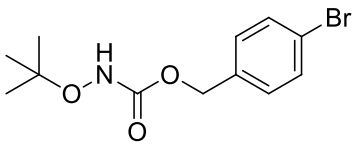
***N*-(*t*-butoxy)carbamate 4.13d** was synthesized in 15 h according to the general procedure and purified by flash chromatography (10% EtOAc in cyclohexane -> 45% EtOAc in cyclohexane, $KMnO_4$). 25 mg (58%) were obtained as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1H), 4.14 (t, *J* = 6.4 Hz, 2H), 2.52 (t, *J* = 7.2 Hz, 2H), 2.15 (s, 3H), 1.92 (quin, *J* = 6.7 Hz, 2H), 1.24 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.74, 158.52, 81.44, 65.00, 39.83, 30.12, 26.31, 23.16. **HRMS** [M + Na^+] calc. for $C_{10}H_{19}NNaO_4$: 240.1206 found: 240.1206.



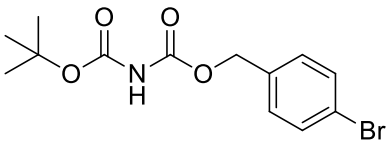
***N*-(*t*-butoxy)carbamate 4.13e** was synthesized in 15 h according to the general procedure and purified by flash chromatography (5% EtOAc in cyclohexane -> 50% EtOAc in cyclohexane, $KMnO_4$). 16 mg (39%) were obtained as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 1H), 4.63 – 4.32 (m, 2H), 3.52 – 3.46 (m, 2H), 1.26 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.83, 81.78, 64.27, 50.19, 26.25. **HRMS** [M + Na^+] calc. for $C_7H_{14}N_4NaO_3$: 225.0958 found: 225.0960.



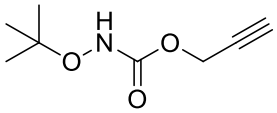
***N*-(*t*-butoxy)carbamate 4.13f** was synthesized in 20 h according to the general procedure and purified by flash chromatography (5% EtOAc in cyclohexane -> 20% EtOAc in cyclohexane, $KMnO_4$). 37 mg (61%) were obtained as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.45 (m, 2H), 7.25 – 7.20 (m, 2H), 7.05 (s, 1H), 5.10 (s, 2H), 1.23 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.18, 134.95, 131.82, 130.05, 122.51, 81.59, 66.67, 26.28. **HRMS** [M + Na^+] calc. for $C_{12}H_{16}BrNNaO_3$: 324.0211 found: 324.0205.



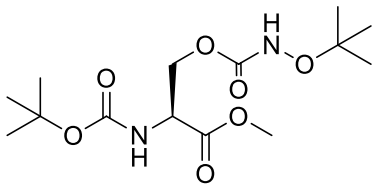
The corresponding side product **biscarbamate 4.14f** eluted just after **4.13f** ($KMnO_4$). Crystallized after flash chromatography from hot cyclohexane at room temperature. Spectra contain grease impurities from cyclohexane.

^{1}H NMR (400 MHz, CDCl3) δ 7.51 – 7.47 (m, 2H), 7.27 – 7.23 (m, 2H), 6.89 (s, 1H), 5.13 (s, 2H), 1.48 (s, 9H). **^{13}C NMR** (101 MHz, CDCl3) δ 150.86, 149.29, 134.39, 131.93, 130.29, 122.80, 82.91, 66.88, 28.12. **HRMS** [M + Na^+] calc. for $C_{13}H_{16}BrNNaO_4$: 352.0155 found 352.0156.



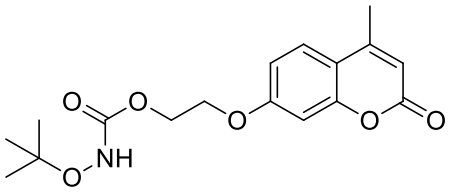
***N*-(*t*-butoxy)carbamate 4.13g** was synthesized in 10 h according to the general procedure using 2.5 eq of K_2CO_3 and purified by flash chromatography (5% EtOAc in cyclohexane -> 15% EtOAc in cyclohexane, $KMnO_4$). 17 mg (50%) were obtained as a colorless oil (SLIGHTLY VOLATILE).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 1H), 4.74 (d, *J* = 2.5 Hz, 2H), 2.49 (t, *J* = 2.5 Hz, 1H), 1.26 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.37, 81.88, 77.60, 75.34, 53.29, 26.27. **HRMS** [M + Na^+] calc. for $C_8H_{13}NNaO_3$: 194.0788 found: 194.0789.



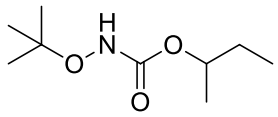
***N*-(*t*-butoxy)carbamate 4.13h** was synthesized in 30 h according to the general procedure with 3 eq of reagent **4.10b** and purified by flash chromatography (5% EtOAc in cyclohexane -> 30% EtOAc in cyclohexane over 17 CV, $KMnO_4$). 27 mg (40%) were obtained as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 1H), 5.36 (d, *J* = 8.1 Hz, 1H), 4.58 – 4.46 (m, 2H), 4.39 (dd, *J* = 11.1, 3.3 Hz, 1H), 3.76 (s, 3H), 1.44 (s, 9H), 1.23 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.38, 157.76, 155.29, 81.74, 80.48, 65.42, 53.32, 52.88, 28.41, 26.25. **HRMS** [M + Na^+] calc. for $C_{14}H_{26}N_2NaO_7$: 357.1632 found: 357.1637. $[\alpha]_D^{20}$ + 12.2 (c 0.53, $CHCl_3$).



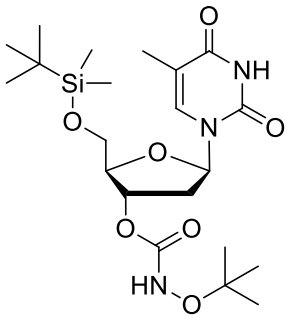
***N*-(*t*-butoxy)carbamate 4.13i** was synthesized in 18 h according to the general procedure and purified by flash chromatography (20% EtOAc in cyclohexane -> 50% EtOAc in cyclohexane, $KMnO_4$). 39 mg (58%) were obtained as colorless oil, slowly forming crystals. Small unknown aliphatic impurities.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.8 Hz, 1H), 7.19 (s br, 1H), 6.85 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.78 (d, *J* = 2.5 Hz, 1H), 6.12 (d, *J* = 1.2 Hz, 1H), 4.52 – 4.48 (m, 2H), 4.24 – 4.20 (m, 2H), 2.38 (d, *J* = 1.2 Hz, 3H), 1.23 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.45, 161.27, 158.04, 155.23, 152.57, 125.78, 114.06, 112.43, 112.32, 101.74, 81.70, 66.63, 63.52, 26.24, 18.76. **HRMS** [M + Na^+] calc. for $C_{17}H_{21}NNaO_6$: 358.1267 found: 358.1262.



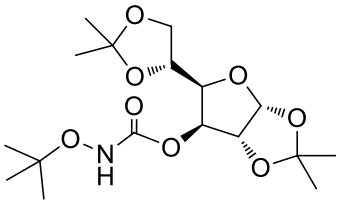
***N*-(*t*-butoxy)carbamate 4.13j** was synthesized in 20 h according to the general procedure and purified by flash chromatography (5% EtOAc in cyclohexane -> 10% EtOAc in cyclohexane, $KMnO_4$). 18 mg (48%) were obtained as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 1H), 4.84 – 4.75 (m, 1H), 1.66 – 1.49 (m, 2H), 1.24 (s, 9H), 1.22 (d, *J* = 6.3 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.51, 81.21, 74.13, 29.05, 26.33, 19.69, 9.71. **HRMS** [M + Na^+] calc. for $C_9H_{19}NNaO_3$: 212.1263 found: 212.1259.



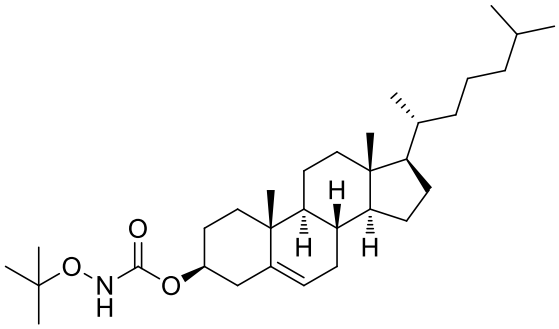
***N*-(*t*-butoxy)carbamate 4.13k** was synthesized in 15 h according to the general procedure with 3 eq of reagent **4.10b** and purified by reversed phase preparative HPLC (MeCN / H_2O, 2% to 80% over 28 min, 254 nm, t_R = 28 min). 55 mg (52%, effective) were obtained as white solid, containing 10% of the discussed byproduct.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.54 (d, *J* = 1.2 Hz, 1H), 7.14 (s, 1H), 6.35 (dd, *J* = 9.4, 5.1 Hz, 1H), 5.24 (d, *J* = 5.8 Hz, 1H), 4.16 – 4.14 (m, 1H), 3.97 – 3.88 (m, 2H), 2.42 (dd, *J* = 13.7, 5.2 Hz, 1H), 2.11 (ddd, *J* = 13.8, 9.4, 6.0 Hz, 1H), 1.92 (d, *J* = 1.1 Hz, 3H), 1.26 (s, 9H), 0.92 (s, 9H), 0.13 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.68, 157.60, 150.45, 135.16, 111.39, 85.61, 84.80, 81.86, 76.96, 63.74, 38.18, 26.31, 26.07, 18.46, 12.64, -5.24, -5.33. **HRMS** [M + Na^+] calc. for $C_{21}H_{37}N_3NaO_7Si$: 494.2293 found: 494.2297.



***N*-(*t*-butoxy)carbamate 4.13l** was synthesized according to the general procedure. 2 eq of reagent **4.10b** and 5 eq K_2CO_3 were used and the reaction stirred for 16 h. Then another 2 eq of **4.10b** were added. Efficient stirring was important. After another 2h another 2 eq of **4.10b** were added. ^{1}H NMR reaction control suggested 45% conversion of the alcohol. Purified by flash chromatography (10% EtOAc in cyclohexane -> 30% EtOAc in cyclohexane, $KMnO_4$). 32 mg (34%, effective) were obtained as colorless oil in 80% purity. An analytical sample was obtained by preparative HPLC (MeCN / H_2O, 2% to 70% over 25 min, 190 nm, t_R = 24 min).

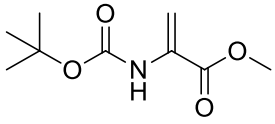
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 1H), 5.89 (d, *J* = 3.7 Hz, 1H), 5.25 (d, *J* = 1.9 Hz, 1H), 4.59 (d, *J* = 3.7 Hz, 1H), 4.27 – 4.21 (m, 2H), 4.14 – 4.09 (m, 1H), 4.06 – 4.01 (m, 1H), 1.54 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H), 1.27 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.99, 112.48, 109.49, 105.14, 83.43, 81.77, 79.99, 77.51 (HMQC), 72.56, 67.32, 26.94, 26.87, 26.34, 26.30, 25.40. **HRMS** [M + Na^+] calc. for $C_{17}H_{29}NNaO_8$: 398.1785 found: 398.1786. **$[\alpha]_D^{20}$** – 16.5 (c 0.51, $CHCl_3$).



***N*-(*t*-butoxy)carbamate 4.13m** was synthesized in 26 h according to the general procedure and purified by flash chromatography (1% EtOAc in cyclohexane -> 8% EtOAc in cyclohexane, $KMnO_4$). 65 mg (58%, effective) were obtained as a white solid containing 10% of the discussed side product.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (s, 1H), 5.38 – 5.35 (m, 1H), 4.60 – 4.51 (m, 1H), 2.38 (ddd, *J* = 13.0, 5.1, 2.1 Hz, 1H), 2.34 – 2.26 (m, 1H), 2.03 – 1.77 (m, 5H), 1.63 – 1.41 (m, 7H), 1.38 – 1.30 (m, 3H), 1.24 (s, 9H), 1.19 -1.01 (m, 8H), 1.00 (s, 3H), 0.98 – 0.92 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 2.3 Hz, 3H), 0.85 (d, *J* = 2.3 Hz, 3H), 0.67 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.12, 139.62, 122.91, 81.29, 75.71, 56.79, 56.25, 50.11, 42.43, 39.84, 39.64, 38.41, 37.05, 36.66, 36.30, 35.92, 32.01, 31.97, 28.35, 28.14, 28.06, 26.34, 24.40, 23.96, 22.95, 22.69, 21.16, 19.44, 18.84, 11.98. **HRMS** [M + Na^+] calc. for $C_{32}H_{55}NaNO_3$: 524.4080 found: 524.4079.

5.5.6 Dehydroalanine



Under the synthesis and purification conditions for *N*-(*t*-butoxy)carbamate **4.13h**, **dehydroalanine 4.15** eluted after 2 CV. Analytical data was in agreement with the reported data by Xian[152]

5.5.7 Crystallographic data

Crystal data for **4.14f**: formula $C_{13}H_{16}Br_1N_1O_4$, M = 330.18, F(000) = 2016, colorless plate, size 0.01·0.09·0.17 mm^3, orthorhombic, space group P n a 2_1, Z = 12, a = 8.2877(3) Å, b = 21.9834(13) Å, c = 23.8023(11) Å, α = 90°, β = 90°, γ = 90°, V = 4336.6(2) $Å^3$, $D_{calc.}$ = 1.517 Mg · m^{-3}. The crystal was measured on a Bruker Kappa Apex2 diffractometer at 123K using a Cu K_α-microsource with λ = 1.54178 Å, $Θ_{max}$ = 69.116°. Minimal/maximal transmission 0.70/0.96, μ = 3.976 mm^{-1}. The Apex2 suite has been used for datacollection and integration.[189] From a total of 19231 reflections, 6797 were independent (merging r = 0.083). From these, 4185 were considered as observed (I>1.2σ(I)) and were used to refine 515 parameters. The structure was solved by the charge flipping method using the program Superflip.[190] Least-squares refinement against F was carried out on all non-hydrogen atoms using the program CRYSTALS.[191] R = 0.1589 (observed data), wR = 0.1352 (all data), GOF = 1.0665. Minimal/maximal residual electron density = -2.29/2.02 e $Å^{-3}$. Chebychev polynomial weights[192] were used to complete the refinement. Plots were produced using Mercury. ENREF 194[193] Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Center, the deposition number is 1054602. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

The solution and refinement of this structure presented various problems. Determining the unit cell after harvesting reflections with I>12σ(I) gave an orthorhombic unit cell with a = 8.2888(3) Å, b = 7.3261(4) Å and c = 23.8048(9) Å. Repeating the same using reflections with I>6σ(I) gave equally an orthorhombic unit cell, but this time with unit cell parameters of a = 8.2877(3), b = 21.9834(13) and c = 23.8023(11), thus the b axes was now three times as long as in the first try.

The crystals showed moderate diffraction power. Integration was performed using both unit cells. In both cases the structure could be solved without big problems.

Using the data set from the big unit cell the refinement was very difficult as three formally symmetry independent molecules are present in the asymmetric unit. Due to the pseudo-translational symmetry two thirds if the reflections are weakened, resulting in a poor number of observed reflections. Moreover the models of the three molecules are highly correlated due to this almost perfect translational symmetry, which caused the refinement to be instable.

In contrast to this problematic behavior the refinement using the data set from the small unit cell was straight forward (r = 0.0622 for data with I>2σ(I)), with the only problem that the displacement parameters of the Br-atom got huge. Assuming a disorder that involves the heaviest atom of the

structure was highly unlikely to be true. For this reason the refinement was continued with the data set from the big unit cell.

Restraining distances, angles and displacement parameters to their respective common means of all three molecules refinement could be finished. The R-value is higher than desired. For the residual electron density the same is true. But still this structure is nearer to reality than the one with the short b axes as the differences, in particular those linked with the Br-atom are too big to be averaged. For this reason the refinement using the data from the big unit cell was retained for publication.

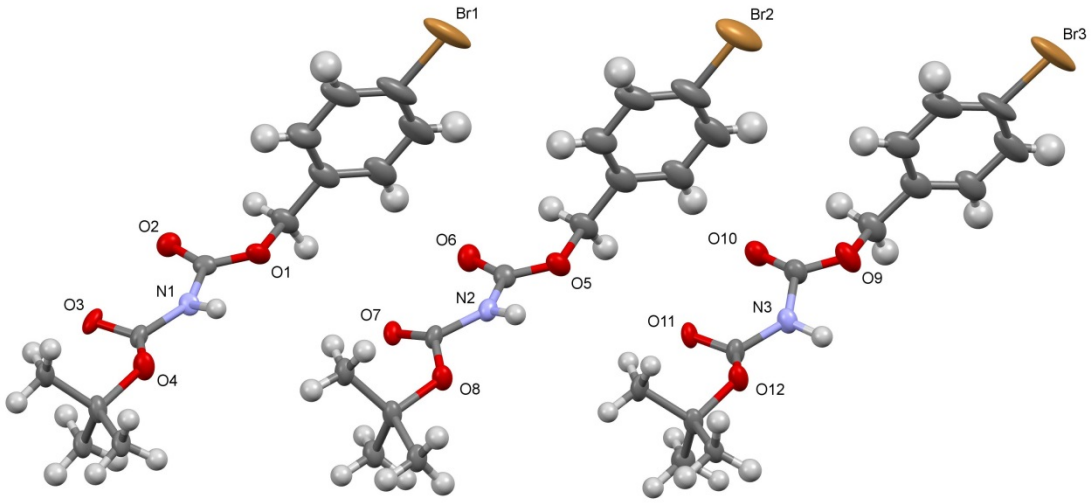


Figure 5-1: Ellipsoid plot of the structure of 4.14f

5.6 List of abreviations

acac	acetyl acetonate
AD-mix	$(DHQ)_2PHAL$ alkaloid, K_2CO_3, $K_4Fe(CN)_6$, K_2OsO_4
BPO	benzoyl peroxide
BSA	*N*,*O*-bistrimethylsilyl acetamide
CAN	ceric ammonium nitrate $(NH_4)_2Ce(NO_3)_6$
cap	caprolactamate
CDI	1,1‘-carbonyldiimidazole
CV	column volumes
DNA	deoxyribonucleic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIPEA	*N*,*N*-diisopropylethylamine
DIPA	*N*,*N*-diisopropylamine
DMAP	4-dimethylaminopyridne
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1‘-bis(diphenylphosphino)ferrocene
dppp	1,1‘-bis(diphenylphosphino)propane
eq	equivalent(s)
HMPA	hexamethylphosphoramide
HPLC	high pressure liquid chromatography
IBX	2-iodoxybenzoic acid
LAH	lithium aluminium hydride
LDA	lithiumdiisopropylamide
LNA	locked nucleic acid
MOM	methoxymethyl (ether)
Ms	mesylate
NBS	*N*-bromosuccinimde
NMR	nuclear magnetic resonance (spectroscopy)
Pin	pinacolate
PPTS	pyridinium *p*-toluenesulfonate
PTSA	*p*-toluenesulfonic acid
RNA	ribonucleic acid
TASF(Et)	tris(diethylamino)sulfonium difluorotrimethylsilicate
TBAC	*N*,*N*,*N*,*N*-tetra *n*-butylammonium chloride
TBHP	*t*-butyl hydroperoxide
TBS	*t*-butyldimethyl silyl (ether, chloride, triflate,…)
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	tri *i*-propylsilyl (ether, chloride, triflate,…)
TMS	trimethylsilyl (ether, chloride, triflate,…)
Ts	tosylate
UPLC-MS	ultra pressure liquid chromatography, mass spectroscopy

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