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Doctoral Dissertation

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Abstract

Amaminols A and B are cytotoxic bicyclic aminoalcohols isolated in 1999 from an unidentified tunicate of the family *Polyclinidae*, with an IC_{50} value of 2.1 μg/mL against P_{388} murine leukaemia cells. These cytotoxic properties could have potential importance in the development of new therapeutical agents for cancer treatment. Since the source of amaminols is practically unknown, the development of a practical synthesis route is probably the only way to obtain material for further evaluation of biological activities of these compounds.

This thesis describes the total synthesis of amaminol A using an enantioselective organocalalytic intramolecular Diels-Alder reaction as one of the key steps. The full carbon skeleton of amaminol A is constructed using the Horner-Wadsworth-Emmons reaction of a phosphonate derived from natural amino acid L-alanine. Strategic reduction with copper hydride proved to be highly important and led to further development of this technology. Final reduction followed by removal of protections gave synthetic amaminol A, which was found to be identical with the isolated natural product. Our synthetic amaminol A was tested against various cancer cell lines at the National Cancer Institute.

The second part of this thesis focuses on copper hydrides. The literature part presents an extensive review of achiral phosphine stabilized copper hydrides used in conjugate reductions of various α,β-unsaturated systems. Further development by us led to a highly selective method for reduction of α-chiral enones. This was also the first phosphite stabilized copper hydride methodology used in synthesis. Applicability of this new method was demonstrated in the synthesis of amaminol A.

The third part of the thesis describes mechanistic studies of aerobic oxidations of alcohols catalyzed by copper-TEMPO system. Detailed evaluation of different catalyst components revealed second order kinetic correlation for copper and first order correlation for TEMPO. This information was used to generate a new mechanistic proposal which was in agreement with the obtained kinetic data. Oxidation of allylic primary alcohols with $CuBr_2$-TEMPO system was found to be highly efficient. Oxidation of aliphatic alcohols proved to be more challenging and required the use of copper triflate.

Keywords amaminol, total synthesis, biological activity, copper hydride, oxidation

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Tiivistelmä

Amaminolit A ja B ovat bisyklisiä aminoalkoholeja, jotka eristettiin vuonna 1999 tunnistamattomasta *Polyclinidae* suvun vaippaeläimestä. Amaminolien on havaittu estävän hiiren P_{388} leukemiasolujen kasvua IC_{50} arvolla 2.1 µg/mL. Tämä bioaktiivisuus voi osoittautua hyödylliseksi uusien syöpälääkkeiden kehityksessä. Amaminolien luonnollinen lähde on käytännössä tuntematon, joten kokonaissynteesi on ainoa käytännöllinen tapa tuottaa ainetta bioaktiivisuuden jatkotutkimuksiin.

Tässä väitöskirjassa kuvataan amaminol A:n ensimmäinen kokonaissynteesi, jonka eräänä avainreaktiona oli enantio-selektiivinen organokatalyyttinen Diels-Alder reaktio. Hiiliketju täydennettiin käyttämällä Horner-Wadsworth-Emmons reaktiota, johon käytettiin luonnollisesta L-alaniinistä johdettua fosfonaattia. Strategisesti tärkeä konjugaattipelkistys tehtiin kuparihydridin avulla. Viimeinen stereokeskus tehtiin diastereoselektiivisellä pelkistyksellä, jonka jälkeen typen suojaryhmä poistettiin. Täten saatiin synteettinen amaminoli A, jonka spektridatan havaittiin olevan yhtenevä luonnosta eristetyn aineen kanssa. Synteettinen amaminoli testattiin yhdysvaltain National Cancer Institutessa useita eri syöpäsolulinjoja vastaan.

Väitöskirjan toinen osio keskittyy kuparihydrideihin. Kirjallisuusosiossa esitellään kattava tietopaketti kirjallisuudessa esiintyvien fosfiinistabiloitujen kuparihydridien käytöstä erilaisten systeemien konjugaattipelkistyksissä. Havaittuamme puutteen käytettävissä olevista metodeista, kehitimme itse selektiivisen pelkistyksen α-kiraalisille enoneille. Samalla tulimme kehittäneeksi ensimmäisen synteesimenetelmän, jossa kuparihydridi on stabiloitu fosfiitilla. Lopuksi osoitimme tämä uuden menetelmän käytettävyyden amaminoli A:n synteesissä.

Väitöskirjan kolmannessa osiossa esitetään mekanistinen tutkimus kupari-TEMPO katalysoitujen alkoholien hapetuksessa käyttäen happea terminaalisena hapettimena. Katalyyttikomponenttien merkityksen tutkimus osoitti kuparin määrän noudattavan toisen asteen kinetiikkaa. TEMPO-kofaktorin havaittiin puolestaan noudattavan ensimmäisen asteen kinetiikkaa. Tutkimuksen perusteella luotiin uusi mekanistinen esitys, joka noudattaa mitattua informaatiota. Allyylisten alkoholien hapettaminen onnistui tehokkaasti $CuBr_2$-TEMPO katalyysillä. Alifaattisten alkoholien hapettaminen oli haastavampaa ja vaati kuparilähteen vaihtamisen kuparitriflaattiin.

Asiasanat amaminol, kokonaissynteesi, biologinen aktiivisuus, kuparihydridi, hapetus

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I wish to thank my supervisor Professor Ari Koskinen for welcoming me into his research group and allowing me to find myself some challenging research targets. I have learned a lot from him in his lecture courses and later by conducting research under his supervision. His knowledge in organic synthesis and in general chemistry is truly impressive.

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Prof. Martin E. Maier and Prof. Philippe Renaud have carefully checked the manuscript and M.Sc. Antti Kataja aided in revising the language of the thesis.

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I want to thank my family: parents Heikki and Helena and my sisters Päivi, Sirpa and Sirke for their support. The Sippala family: Mauno, Arja, Ville, Jussi, Vivi deserve special thanks for support and help during my life.

Dear friends, I want to thank you the most since you have kept me sane during these years. Jarkko, Teemu, Kaitsu and Ville were my support network during my childhood. My game crew: Tane, Jani, Niko, Repo, Anssi, Karvo and Paunonen kept me company during my school years. We have really had fun with my ballooning crew: Samppa, Tomppa and Kapu. And finally to my choir, Hämäläis-Osakunnan Laulajat (HOL) and friends there have allowed me to learn musical skills and kept me out of the work every Tuesday evening.

I dedicate this thesis to Iris Kumpulainen and Mauno Sippala.

Espoo, March 2010

Esa Kumpulainen

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AUTHOR'S CONTRIBUTION

The author, Esa Kumpulainen designed, carried out the experiments, analysis and interpreted the results that are presented in this work. Certain part of the work was done by other researchers in collaboration with the author. To specify, Professor Kari Rissanen analyzed the crystal structure of a derivative of amaminol A shown in Figure 7. Biological data for amaminol A was measured by an unknown person(s) in the National Cancer Institute, USA. Graduate student Andrejs Pelšs is responsible of the optimization of copper hydride reactions shown in Table 5. The author designed the work related to copper hydrides with A. P. and was responsible of instructing him in the practical research. The solvent screen for the copper-catalyzed aerobic oxidations, shown in Figure 27, was done by undergraduate student (presently M. Sc.) Kalle Kettunen under the supervision of the author.

Publications related to this work are written by the author together with co-authors.[16,136,167]

ABBREVIATIONS AND DEFINITIONS

A	general acid
Ac	acetyl
AIBN	azobisisobutyronitrile
(*S*)-Alpine hydride	lithium *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonyl hydride
BAIB	[bis(acetoxy)-iodo]benzene
o-BDPPB	1,2-bis(diphenylphosphino)benzene
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
t-Bu	*tert*-butyl
Bn	benzyl
BiPy	2,2'-bipyridine
bpy	2,2'-bipyridine
Bz	benzoyl
CDI	carbonyl diimidazole
CSA	camphorsulfonic acid
Cy	cyclohexyl
de	diastereolectivity
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMA	*N,N*-dimethylacetamide
DMAP	*N,N*-dimethyl aminopyridine
DMF	*N,N*-dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DPEphos	2,2'-bis(diphenylphosphino)-diphenyl ether
dppb	1,1'-bis(diphenylphosphino)butane

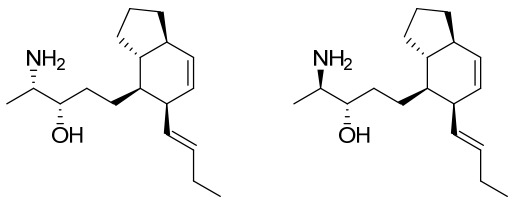
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,1'-bis(diphenylphosphino)propane
EDG	electron donating group
ee	enantioselectivity
Et	ethyl
(*S,S*)-Et-DuPhos	(+)-1,2-bis[(2*S*,5*S*)-2,5-diethylphospholano]benzene
ER	endoplasmic reticulum
EWG	electron withdrawing groug
GO	galactose oxidase
GC	gas chromatograph
HMTS	1,1,3,3,5,5-Hexamethyltrisiloxane
HOMO	highest occupied molecular orbital
HWE	Horner-Wadsworth-Emmons reaction
IBX	2-iodoxybenzoic acid
IMDA	intramolecular Diels-Alder reaction
KHMDS	potassium hexamethyldisilazane
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
Me	methyl
MeCN	acetonitrile
MOM	methoxymethyl
MS	mass spectrometer
NADPH	nicotinamide adenine dinucleotide phosphate, reduced form
NHC	*N*-heterocyclic carbene
NMI	*N*-methyl imidazole
NMP	*N*-methyl-2-pyrrolidinone
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
phen / Phen	phenanthroline
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PMHS	polymethylhydrosiloxane
Proton sponge	1,8-bis(dimethylamino)naphthalene
PT	1-phenyl-1*H*-tetrazol-5-yl

R	arbitrary substructure
S1P	sphingosine-1-phosphate
L-Selectride	lithium tri-*sec*-butylborohydride
SphK	sphingosine kinase
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TEA	triethylamine
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl, free radical
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triphenylsilyl
TMDS	tetramethyldisiloxane
Tol-BINAP	2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl
Tr	triphenylmethyl
Ts	tosyl
p-TsOH	*para*-toluenesulfonic acid
rfx	reflux
rt	room temperature
X	conjugate base of an acid
xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

1 AMAMINOLS

1.1 Introduction

Amaminols A **1** and B **2** are cytotoxic bicyclic aminoalcohols isolated in 1999 from an unidentified tunicate of the family *Polyclinidae* (Figure 1),[1] with an IC_{50} value of 2.1 μg/mL against P_{388} murine leukaemia cells. These compounds contain an interesting hexahydroindene substructure, which induces a tight turn into the carbon chain and therefore reduces the amount of accessible conformations. Such structural restrictions make amaminols very interesting targets for organic synthesis and biological activity studies.



Amaminol A (**1**) Amaminol B (**2**)

Figure 1. Structure of amaminols.

Amaminols are closely related to other sphingoid bases such as xestoaminols,[2] halaminols,[3] crucigasterins,[4] obscuraminols[5] and sphingosines[6] (Figure 2). Sphingoid bases are very important factors in cell membranes where they act as membrane building blocks and participate in molecular signalling. These compounds exist in four possible enantiomeric forms (*2S,3S*), (*2S,3R*), (*2R,3S*), (*2R,3R*) and are generally derived form glycine, alanine and serine. Sphingoids derived from natural L-amino acids are dominant. Interestingly, amaminol A **1** is derived from L-alanine whereas amaminol B **2** comes from the non-natural D-alanine. Another interesting observation can be made when amaminols are compared to obscuraminol A **12** and crucigasterin 277 **13**. All these compounds share the same molecular formula $C_{18}H_{29}NO$ and therefore the same oxidation state. We can envision that if the double bonds in obscuraminol A **12** and crucigasterin 277 **13** are isomerized in such a way that an

intramolecular Diels-Alder reaction could occur, these compounds would be precursors for amaminols A **1** and B **2**.

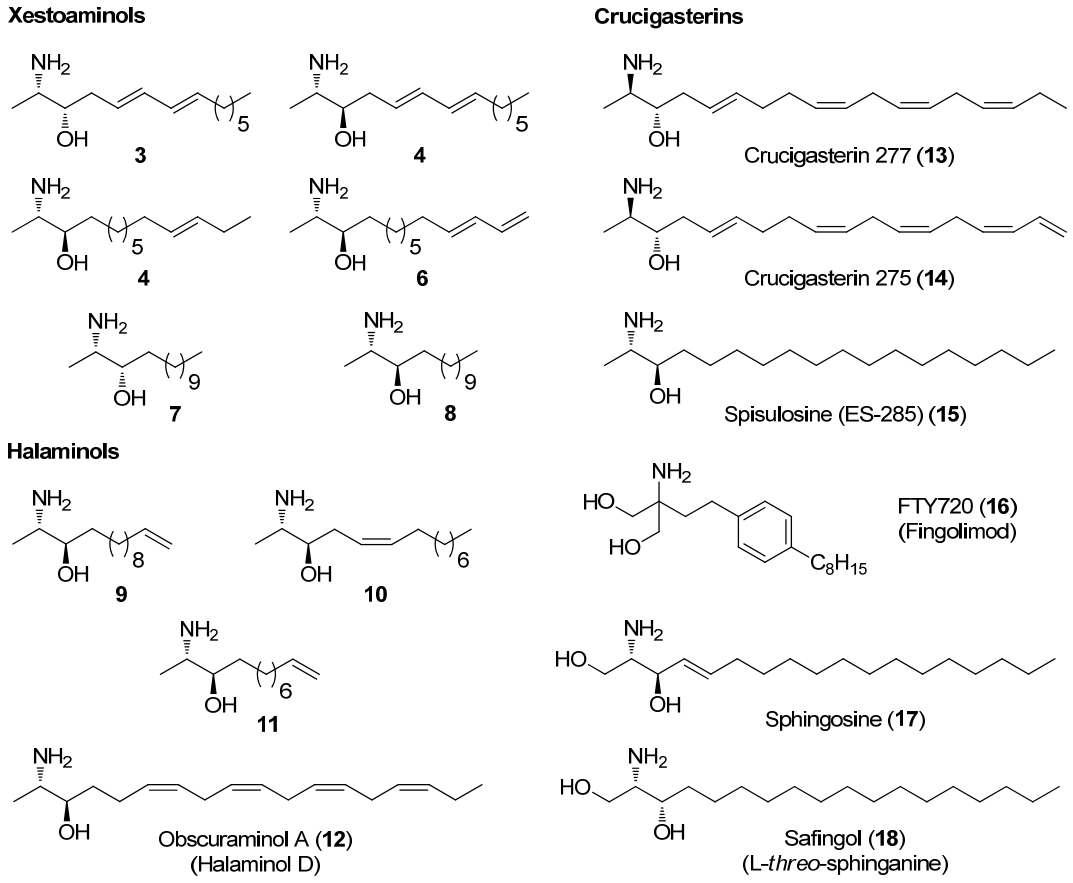


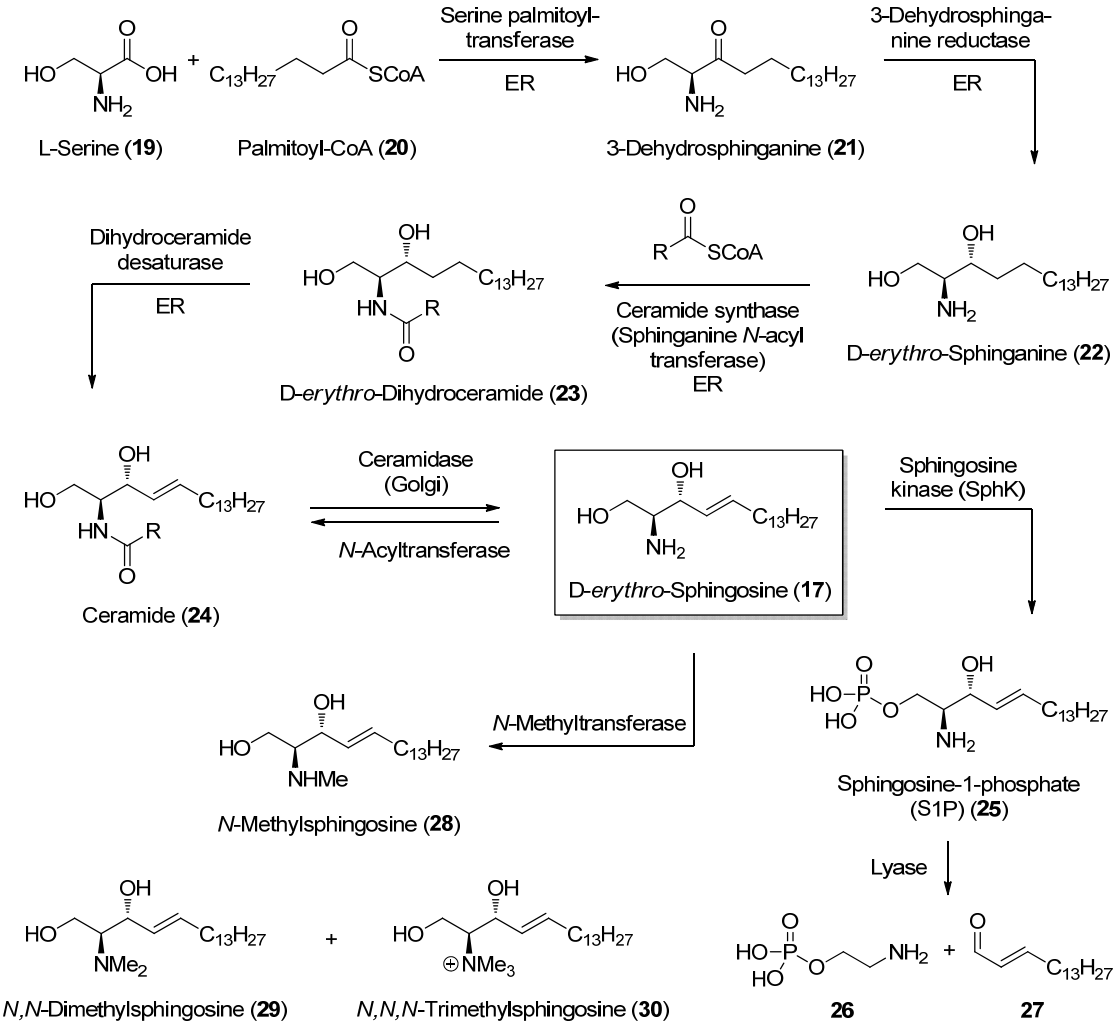
Figure 2. Sphingoid bases and therapeutical agents.

1.2 Biological pathways of sphingosine

Amaminols were found to be biologically active compounds with some cytotoxic properties. The role of their action in cells is not known. In order to understand the biological environment around sphingoid bases, it is reasonable to compare these actions to biological events of the most studied sphingoid, sphingosine **17**.

In the first step of the sphingosine **17** biosynthesis serine palmitoyltransferase is joining L-serine **19** and palmitoyl coenzyme A **20** and releasing carbon dioxide in the process (Scheme 1).[7,6c] 3-Dehydrosphinganine **21** which is formed in the reaction, is then reduced by 3-dehydrosphinganine reductase using nicotinamide adenine dinucleotide phosphate, reduced form (NADPH) as reductant, thus forming D-*erythro*-sphinganine **22**. This reduction determines the stereochemistry at C3 and thus explains why both

isomers at C3 are found in sphingoid bases. Ceramide synthase *N*-acylates sphinganine to form D-*erythro*-dihydroceramide **23**. Reduction of this compound gives ceramide **24**, which is a major component in cell membranes. Ceramide synthesis occurs in the endoplasmic reticulum (ER). In order to form sphingosine **17**, ceramide must be transferred to Golgi apparatus where it is deacetylated by the ceramidase enzyme. Sphingosine **17** exists only in very small quantities in biological systems. It can be transferred back to ceramide **24** by *N*-acyltransferase. Most of the formed sphingosine **17** is rapidly converted to sphingosine-1-phosphate (S1P) **25** or *N*-methylated to various *N*-methyl sphingosines **28-30**.



Scheme 1. Sphingosine **17** *de novo* synthesis and some metabolic pathways.

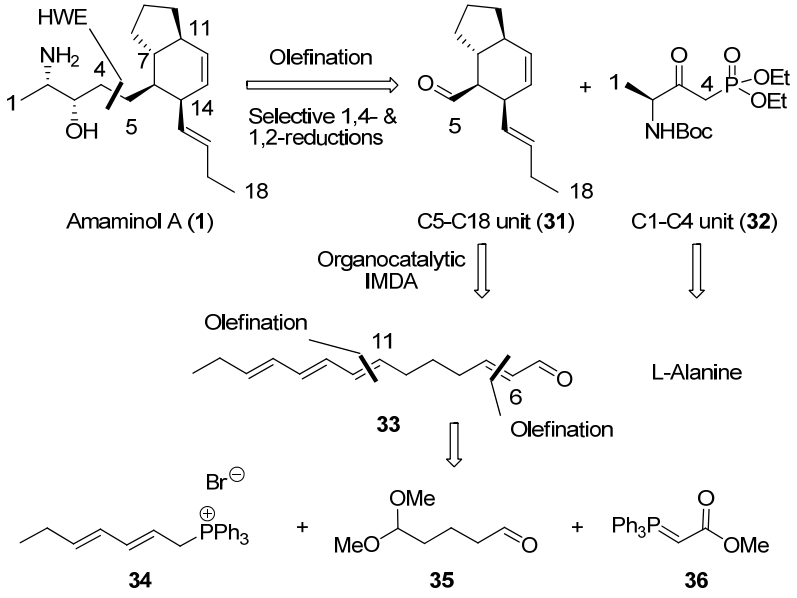
After sphingosine **17** was found to inhibit protein kinase C, it was postulated that sphingoid-derived compounds might act as secondary messengers.[8] This is indeed the case, and the most intriguing metabolite is sphingosine-1-phosphate **25** (S1P), which is

responsible for the regulation of cell growth, cell survival, cell invasion, vascular maturation and angiogenesis.[9] It has been shown that cancer cells use S1P as a signaller, which binds to $S1P_1$-reseptors in endothelial cells and activate vascular endothelial growth factors (VEGF).[10] Sphingosine metabolites may act as therapeutic agents, since *N,N*-dimethylsphingosine **29** has been found to be cytotoxic for many cancer cell lines,[11] and *N,N,N*-trimethylsphingosine **30** has been shown to reduce myocardial infarct size and improve cardiac function.[12]

Due to these findings, there is an increasing interest to develop sphingoid base analogues for pharmaceutical use. One such compound is FTY720 **16**, which was originally developed as a palmitoyltranferase inhibitor (Figure 2). It did not inhibit this enzyme, but it was found to have immunosuppressant activity. FTY720 **16** is phosphorylated by sphingosine kinase (SphK) and it then acts as both an agonist for S1P-reseptors and an antagonist to subtype $S1P_1$-reseptor. Phase III clinical trials showed that FTY720 **16** was not able to improve immunosuppressant activity in kidney transplantations compared to existing drugs.[13] However, phase II clinical trials have shown encouraging results on the treatment of multiple sclerosis. Safingol **18** is another synthetic sphingosine analogue, which has shown anti-tumor activity in phase I clinical trials, when used with another agent such as mitomycin C and ferentinide.[14] Safingol **18** is acylated by ceramidase synthase and *N*-methylated by methyltransferases. 1-Deoxysphingoids are interesting analogs of sphingosine since these compounds cannot be phosphorylated by SphK, which could then lead to degradation by lyases. One such compound is spisulosine (ES-285) **15,** which inhibits proliferation of multiple cancer cell lines.[15] Its biological mechanism is not known, but it is rapidly acylated by ceramidase synthase, which might induce cell death. Amaminols are also 1-deoxysphingoids and their metabolism is thought to be similar.

2 TOTAL SYNTHESIS OF AMAMINOL A

Amaminol A **1** is an amino alcohol which consists of six stereocenters. Retrosynthetic analysis reveals a route based on three consecutive olefinations (Scheme 1).[16] The stereogenic center at C2 is derived from L-alanine as would be suggested by biogenesis of sphingosine **17**. The C3 stereocenter was envisaged to be formed through a diastereoselective 1,2-reduction using the chirality derived from L-alanine. The rest of the stereocenters in the C5-C18 unit **31** were to be formed in an enantioselective intra-molecular Diels-Alder reaction of the intermediate aldehyde **33**. Obvious disconnections of **33** lead to the known phosphonium salt **34**,[17] protected glutaraldehyde **35**[18] and commercially available Wittig ylide **36**.

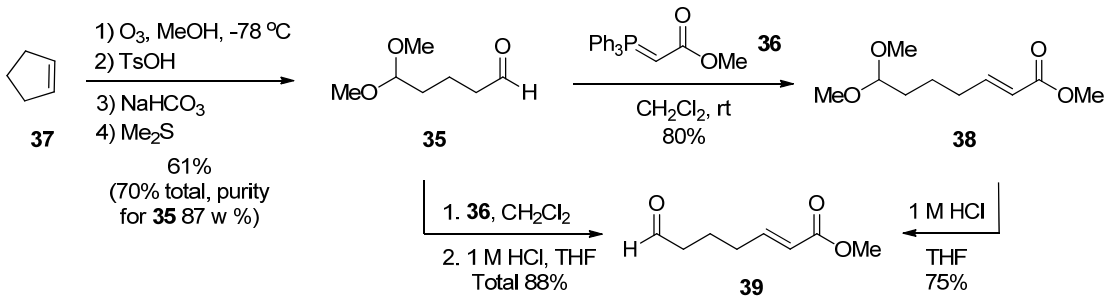


Scheme 2. Retrosynthetic analysis of amaminol A **1**.

2.1 Synthesis of C5-C18 tetraene building block

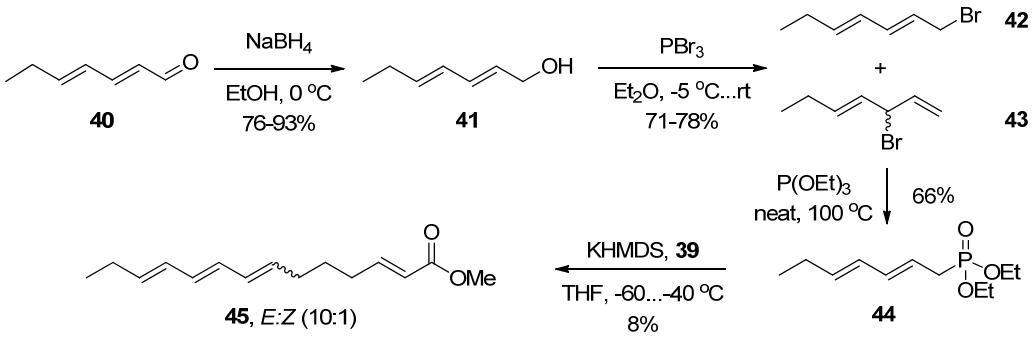
The synthesis of tetraene **33** was started by ozonolysis of inexpensive cyclopentene **37** using literature procedure in 61% yield (Scheme 3).[18] The moderate yield was caused by undesired cyclization to 2,6-dimethoxypyran in the acetalization step. Obtained

aldehyde acetal **35** was reacted with methyl (triphenylphosphoranylidene)acetate **36** in 80% yield after distillation to give the unsaturated ester **38**.[16] Selectivity of the Wittig reaction was found to be 24:1 (*E/Z*). Hydrolysis with aqueous 1 M HCl solution in THF gave aldehyde **39** in 75% yield. Aldehyde **39** is a known compound, and it has been synthesized earlier by using huge excess of glutaraldehyde relative to phosphonium ylide **36** which was added during 75 hours.[19] Therefore I consider this multistep procedure to be more practical. When the Wittig reaction was done without distillation followed by hydrolysis, we obtained aldehyde **39** (20:1, *E:Z*) in 88% yield after distillation starting from **35**.



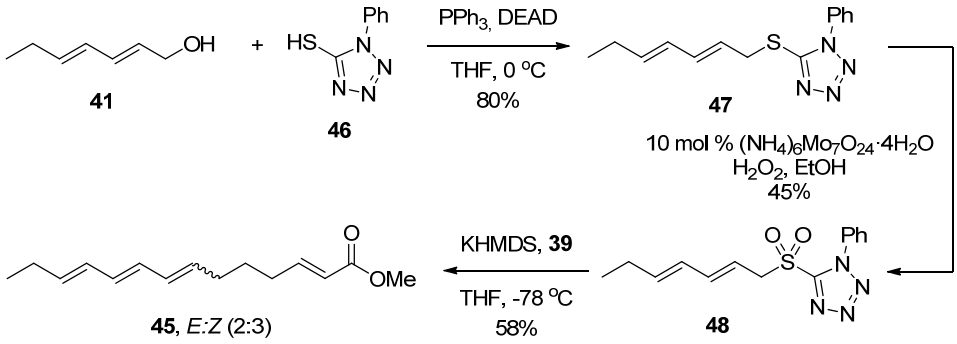
Scheme 3. Early stages in C5-C18 building block synthesis.

The chain elongation was intended to be done by using the Horner-Wadsworth-Emmons reaction (HWE). Phosphonate **44** which was needed for aforementioned reaction was synthesized starting from *E,E*-heptadienal **40** (Scheme 4). Although *E,E*-heptadienol **41** is commercially available, it is seven times more expensive than Kosher grade (>88%) aldehyde **40**. Reduction was performed with sodium borohydride in 93% yield after distillation.[16] Alcohol **41** was transformed into the corresponding allylic bromide with phosphorous tribromide. This procedure gave unfortunately a 2:1 mixture of linear **42** and branched **43** bromides, which could not be separated by distillation and therefore were used as such in the next step. Fortunately, Arbuzov reaction gave the linear phophonate **44** in 66% yield over two steps. HWE reaction was tested using KO*t*-Bu, BuLi, LDA and KHMDS as bases. All of these reactions gave only trace amounts of tetraene **45**. Best results were obtained with KHMDS, which gave only 8% isolated yield. The low yields are probably linked to poor stabilization of phosphonate **44** enolate, which decreases the acidity the α-protons. The corresponding enolate is quenched by the more acidic α-proton found in aldehyde **39**, which also leads to full decomposition of the starting material.



Scheme 4. Chain elongation with HWE reaction.

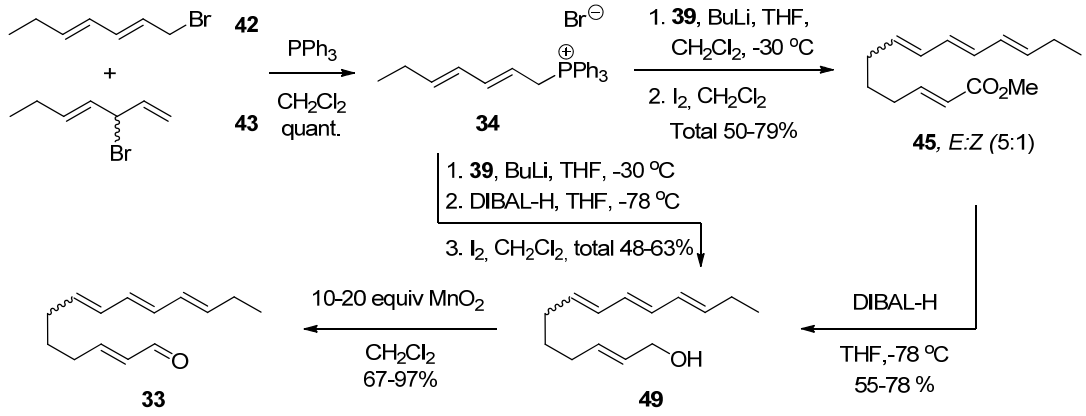
Other highly *E*-selective double bond-forming reactions are for example the Julia olefination and its modification, the Julia-Kocienski olefination. Alcohol **41** was transformed into the corresponding sulfide **47** in 80% yield by using standard Mitsunobu conditions (Scheme 5). This sulfide was oxygenated in the presence of double bonds using ammonium molybdate catalyst and hydrogen peroxide, giving sulfone **48** in a moderate 45% yield. The poor yield might be caused by a [2+3] sigmatropic rearrangement of the intermediate sulfoxide. Readily available aldehyde **39** was coupled with sulfone **48** using KHMDS as the base to give the tetraene **45** in moderate 58% yield. Unfortunately, geometrical selectivity over newly formed double bond was found to be 2:3 (*E:Z*).



Scheme 5. Chain elongation with Julia-Kocienski olefination.

The original synthesis plan was based on Wittig reaction, but it was initially abandoned due to the general *Z*-selectivity of non-stabilized ylides. After all these other problems, the original Wittig-approach combined with iodine treatment was found to be an appealing option. The previously prepared bromide mixture of **42** and **43** was transformed to the linear Wittig-salt **34** by using PPh_3 in dichloromethane.[16] Usage of toluene instead gave an oily reaction mixture, and isolation of the product was found to

be problematic. This Wittig-salt **34** was also found to be highly hygroscopic and it did not form any crystalline compositions, and therefore the product had to be used as such. Combining the previously prepared aldehyde **39** with the crude Wittig-salt **34** using BuLi as the base, the tetraene **45** was obtained in good yield (55-79%) after chromatography. Ratio of newly formed double bond was found to be 2:1 (*E:Z*). Treatment with 5 mol % of iodine over 15 minutes gave a composition of 5:1 (*E:Z*). Finally the tetraene ester **45** was reduced using diisobutylaluminium hydride (DIBAL-H) into the allylic alcohol **49** in an acceptable yield (55-78%). This tetraene alcohol **49** was found to be stable and it solidified at -18 °C to give a white crystalline wax. Upon scale-up we combined the Wittig reaction, reduction and iodine treatment, which reduced the number of purification steps. This sequence afforded a total of 48-63% yield and 4:1 (*E:Z*) ratio for the newly formed double bond. The allylic alcohol **49** was then oxidized with manganese dioxide in dichloromethane into the highly volatile and sensitive aldehyde **33**. This material had to be used immediately or on the next day when kept in freezer.



Scheme 6. Chain elongation with Wittig reaction.

2.2 Organocatalytic intramolecular Diels-Alder reaction

Otto Diels and Kurt Alder discovered a new reaction in 1928, which they called "*diene synthesis*".[20] This reaction was later named the Diels-Alder reaction and it has become a fundamental bond-forming reaction in organic chemistry.[21] From this invention and further development they received a Nobel Prize in chemistry in 1950.

Typically a non-activated diene and a dienophile cannot react without high reaction temperatures. This is caused by a high HOMO-LUMO frontier orbital energy gap between reactants (Figure 3). There are two ways to activate the reactants: the energy of the LUMO in the dienophile can be lowered by introducing an electron withdrawing group (EWG), or the energy of the HOMO in the diene can be raised with an electron donating group (EDG). Reactions with activated reactants still require elevated temperatures. Another option is to further activate the dienophile with general acid catalysis, hydrogen bonding,[22] Lewis acids[23] and iminium ion based catalysis.[24] A thermal Diels-Alder reaction leads to a racemic mixture of products. The formation of new stereocenters can also be directed with internal asymmetric induction, for example by using chiral auxiliaries.[25] Asymmetric catalysis with chiral acids,[26] Lewis acids with chiral ligands[27] or enantiopure amines in the case of iminium catalysis[24] have been shown to give high enantio- and diastereoselectivity.

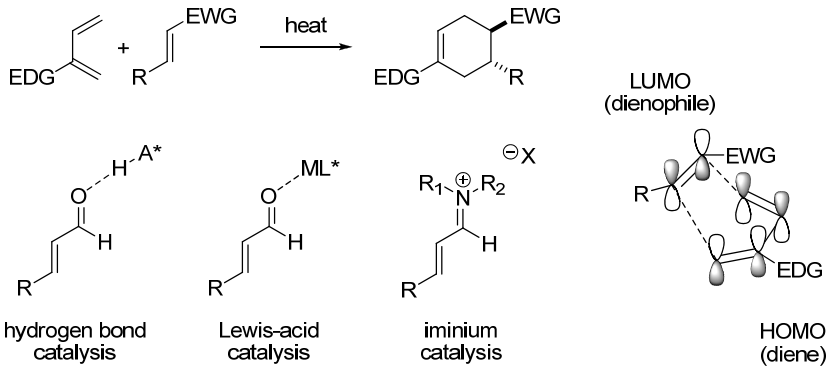
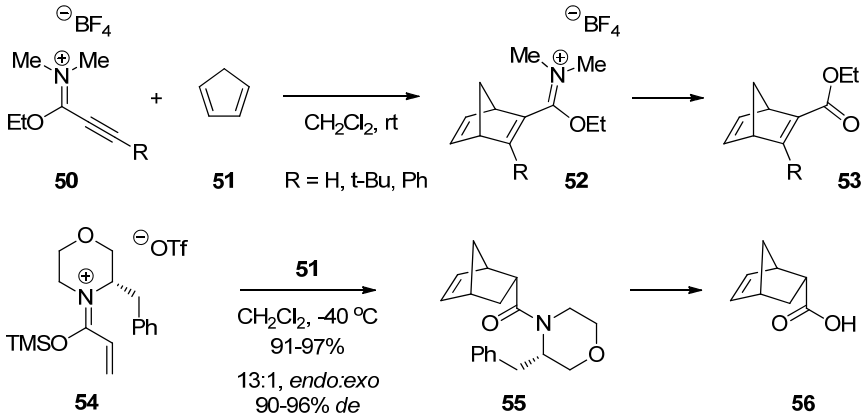


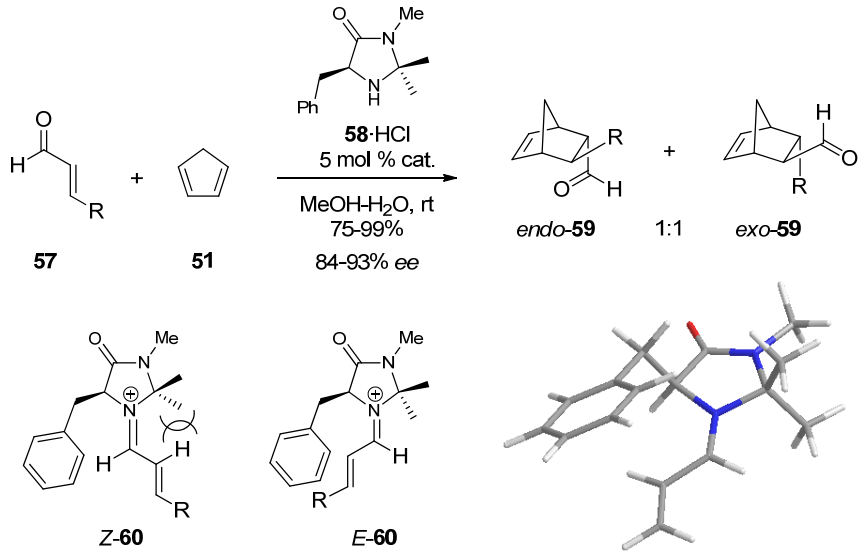
Figure 3. Typical activation modes in Diels-Alder reactions.

The role of iminium catalysis in Diels-Alder reactions was first discovered by Baum and Viehe in 1976 (Scheme 7).[28] They performed reactions of stable acetylenic iminium salts **50** with cyclopentadiene **51** at room temperature and obtained the corresponding cycloaddition products **52**. The first enantioselective version of such a reaction was developed by Jung and co-workers by using L-phenylalanine-derived morpholine.[29] They converted the chiral auxiliary-containing amides *in situ* to TMS-iminium triflate **54**, which was reacted with cyclopentadiene **51** in high diastereoselectivity. Although these reactions were stoichiometric on chiral amines and therefore were diastereoselective reactions, they gave enantiopure products after the hydrolysis of the chiral auxiliary. These findings set the foundations for the development of asymmetric organocatalytic Diels-Alder reactions.



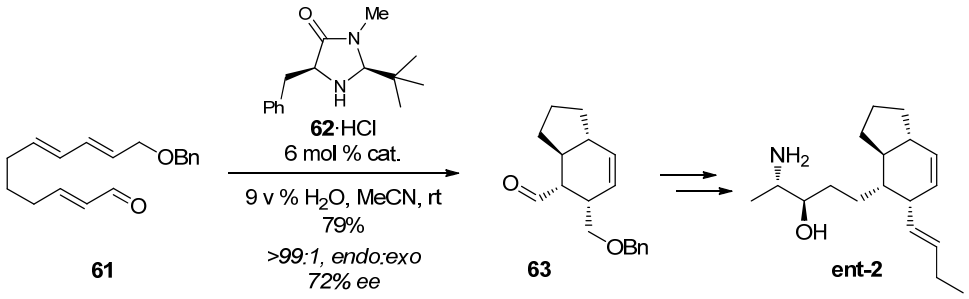
Scheme 7. First iminium catalyzed Diels-Alder reactions.

A major development occurred in 2000, when MacMillan and co-workers reported the first asymmetric organocatalytic Diels-Alder reactions for α,β-unsaturated aldehydes (Scheme 8).[30] They used an imidazolidinone-based catalyst **58** in combination with HCl to catalyze Diels-Alder reactions of aldehydes and various dienes. Enantioselectivities were found to be excellent in these reactions but the *endo:exo* –selectivity was poor. The excellent enantioselectivity can be explained by *E:Z*-selectivity of the iminium ion and facial coverage of phenyl ring in compounds *Z*-**60** and *E*-**60**. In compound *Z*-**60**, the α-proton has unfavourable interactions with the geminal methyl groups of the catalyst **58**. Compound *E*-**60** avoids this interaction and therefore is the dominant species. Benzyl substituent in the catalyst protects the top face of the dienophile and therefore the reaction must occur from the bottom face.



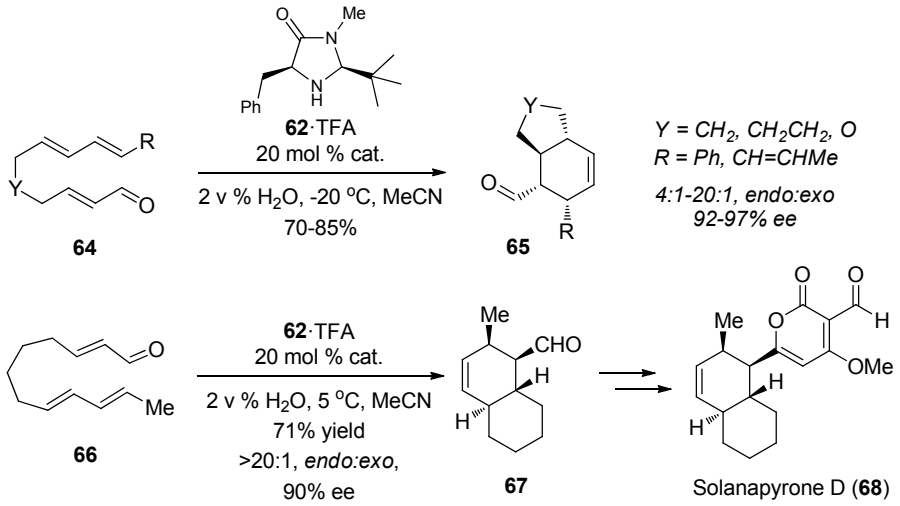
Scheme 8. First organocatalytic Diels-Alder reaction.[30]

My former instructor Sami Selkälä was working on the total synthesis of amaminol A **1** (Scheme 9).[25] After failure of removing the chiral auxiliary after a thermal intramolecular Diels-Alder reaction (IMDA), he got interested in the organocatalytic Diels-Alder reactions developed by MacMillan and co-workers.[30,31] First, he developed a solid-supported catalysts similar to **58**, which was utilized in Diels-Alder reactions.[32] The focus then turned to amaminol A **1** and organocatalytic IMDA. Optimized conditions with catalyst **62**[33] in combination with HCl gave the cyclization product **63** in 72% ee and complete *endo*-selectivity.[34] Unfortunately, the wrong enantiomer of the catalyst **62** was chosen and it led to the enantiomer of amaminol B **ent-2**.[35]



Scheme 9. First organocatalytic intramolecular Diels-Alder reaction.[34]

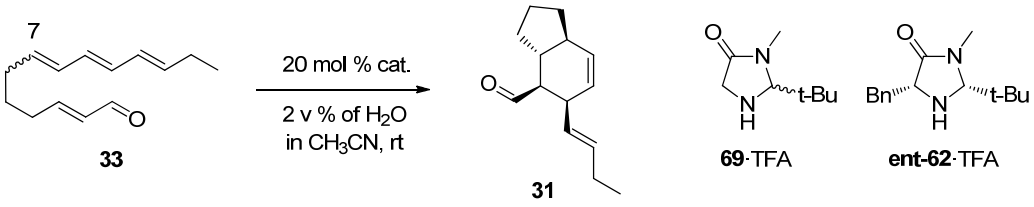
A concurrent study on organocatalytic IMDA by MacMillan and co-workers showed improved enantio- and stereoselectivities (Scheme 10).[36] They used the same catalyst **62** with TFA as co-catalyst instead of HCl. This catalyst system proved to be more generally applicable, as was demonstrated in the total synthesis of solanapyrone D **68**.



Scheme 10. General organocatalytic IMDA and the synthesis of solanapyrone D (**68**).[36]

In the further IMDA studies we chose to use conditions developed by MacMillan, since it gives higher selectivities. The racemic product was done using catalyst **69**, and enantioselective reactions were performed at different temperatures with the catalyst **ent-62**. These results are summarized in Table 1. The C5-C18 core **31** was obtained in 98% ee and full *endo*-selectivity. This key transformation acted also as a kinetic purification, since only the *7E*-isomer **33** was reactive at low temperatures. Such behaviour was also reported by Christmann and co-workers in their synthesis of Lepidopteran sex pheromones.[37]

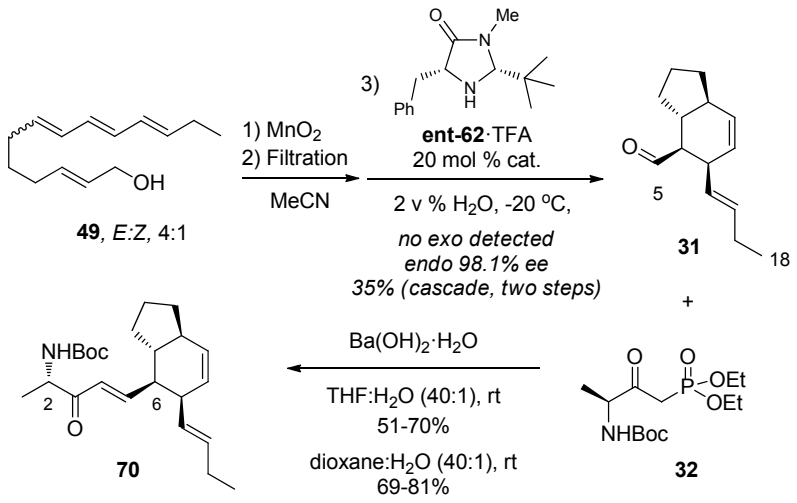
Table 1. Organocatalytic intramolecular Diels-Alder reaction trials.



Entry	Cat.	Mol %	Temp (^{o}C)	Yield **31** (%)	Endo:Exo	Ee %[a]
1	**69**	20	RT	62	12:5	0
2	**ent-62**	20	RT	67	69:1	93.7
3	**ent-62**	20	4	42	308:1	96.6
4	**ent-62**	20	-20	47	100:0	98.1

a) Determined with GC-MS equipped with β-Dex column.

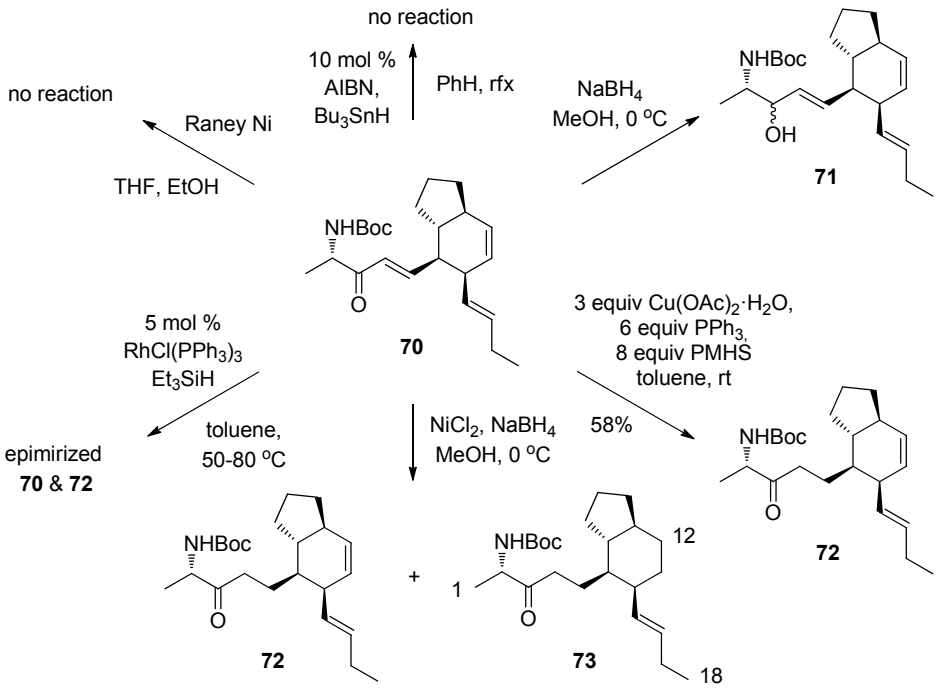
Since the aldehyde **33** was extremely unstable, we decided to avoid isolating it. We found that when conducting the oxidation in acetonitrile, we could filter off the manganese dioxide and then directly continue to the organocatalytic IMDA (Scheme 11).[16] Aldehyde **31** was obtained in 98% ee and 35% yield. HWE reaction using conditions reported by D'Auria and co-workers with known phosphonate **32**[38] gave the full carbon skeleton-containing enone **70** in a moderate yield.[39] We did not observe any epimerization at C2 and C6 stereocenters. Later analysis on the HWE reaction showed that original conditions from Alvarez-Ibarra *et al.* using dioxane gave consistently higher yields (69-81%).[39c] NMR analysis showed identical spectra to those obtained previously. In order to be sure that no epimerization took place, we deliberately epimerized the C6 stereocenter by using K_2CO_3 in ethanol in the HWE reaction[25] and compared the NMR spectral data to those obtained previously.



Scheme 11. Synthesis of C1-C18 amaminol A core.

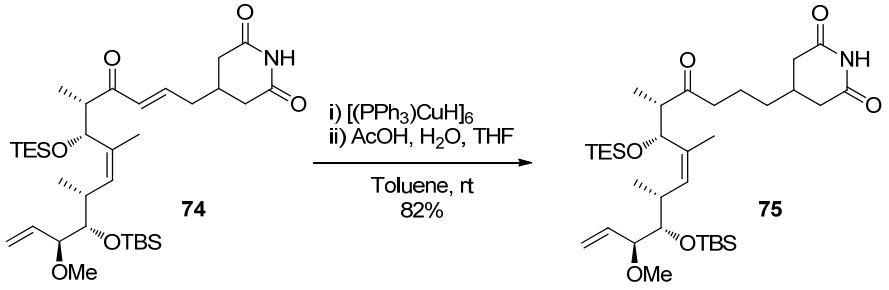
2.3 Selective conjugate reductions

Completion of amaminol A **1** synthesis still required two consecutive reductions. The first reaction is a selective 1,4-reduction of an enone and the second is a chirality-forming 1,2-reduction of a ketone. The enone **70** contains unactivated *cis*- and *trans*-olefins, which should not be reduced and therefore makes these reactions challenging. Selkälä used Raney nickel for the selective conjugate reduction in the synthesis of **ent-2**.[25] Since our group had experience on such a reaction, I also tested these conditions first. Excess amount of commercial Raney nickel extensively washed with ethanol and then added into the reaction failed to give any product (Scheme 12). It seemed that the Raney nickel needed to be freshly prepared. The amount of hydrogen trapped inside Raney nickel cavities is difficult to determine. The high risk of overreduction led us to try other possible methods. A radical reduction with AIBN and Bu_3SnH also failed to give any product.[40] Classical reduction with sodium borohydride led to complete 1,2-selectivity. A reduction with Wilkinson's catalyst [$RhCl(PPh_3)_3$] in combination with triethylsilane as a stoichiometric reductant led to some desired 1,4-reduction but both starting material and product were found to be epimerized.[41] *In situ* generated nickel boride from nickel chloride and sodium borohydride gave an inseparable mixture of **72** and C12-C13 overreduction product **73**.[42]



Scheme 12. Preliminary conjugate reduction trials.

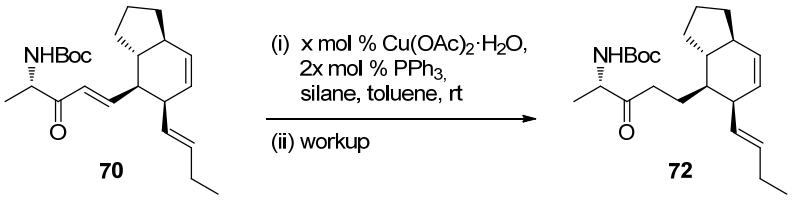
These failed reactions led us to search the literature for alternative reduction methods. We found an interesting example[43] of a selective reduction of an enone in the presence of other unactivated double bonds and a slightly acidic NH-proton, as reported by Danishefsky and co-workers using stoichiometric Stryker's reagent $[(PPh_3)CuH]_6$[44] (Scheme 13). We did not have commercial Stryker's reagent at hand, and the synthesis seemed laborious.[45] An alternative method was proposed by Lee and Yun where Stryker's reagent is generated from $Cu(OAc)_2 \bullet H_2O$ and polymethylhydrosiloxane (PMHS).[46] We thought that this procedure could be used for *in situ* generation of copper hydride, which could then react with enone **70**. Reaction occurred as planned and a clean ketone **72** was obtained in a moderate 58% yield (Scheme 12). Encouraged by the initial experiment using stoichiometric copper hydride, we chose to further focus on this approach.



Scheme 13. Conjugate reduction from Danishefsky and co-workers.[43]

Lipshutz has reported the use of Stryker's reagent as a catalyst and silanes as stoichiometric reductants.[47] Since such an approach seemed more practical, we chose to generate a catalytic amount of Stryker's reagent *in situ* from silanes and then use the same silane as stoichiometric reductant. When the enone **70** was reduced with catalytic copper hydride using $Me(EtO)_2SiH$ as a silane, we could not initially observe any reactivity. Another silane, PMHS, was added and starting material was fully consumed. Finally the reaction was quenched with TBAF and the desired ketone **72** was obtained in a good 80% yield (Table 2, entry 1). When the reaction was repeated using only PMHS, we obtained the ketone **72** in a poorer 50% yield after aqueous workup (entry 2). Some material was lost, and the reaction was repeated combining both TBAF and aqueous workup methods. Excess hydrogen formation was observed when TBAF was added, which also led to major overreduction (entry 3). Reactions with PMHS were difficult to monitor using TLC, since the starting material **70** and product **72** are not separable, and the intermediate silyl enol ethers hydrolyze partially on silica. Poor reproducibility and the reaction monitoring trouble with PMHS led us to test other silanes, such as $Me(EtO)_2SiH$ and $PhSiH_2$ which gave 79% and 60% yields, respectively (entries 4-6). Unfortunately the product ketone **72** was found to be epimerized at C2 stereocenter. Experiment with high excess silanes led to major overreduction and C2-epimerized product **72** (entry 6). Corresponding alcohols were then oxidized back to the ketone **72** using PDC. Since the reoxidized material was not found to be epimerized, we linked the problem to the high basicity of the fluoride ion in corresponding reaction media. The use of high excess of PMHS (8 equiv) had protective characteristics even with TBAF workup and no C2 epimerization was observed in reanalysis of the NMR data of these reactions (entries 1 and 3). Buffering TBAF with acetic acid was found to give non-epimerized products, and it gave the desired ketone **72** in good yields (entries 7-11). When reaction was scaled up (>0.2 mmol), the reproducibility of the reaction was improved and consistent 83-88% yields could be obtained (entries 9-11).

Table 2. Conjugate reduction trials using copper hydride.



Entry	**70** (mmol)	Cat. x (mol %)	Silane (equiv)	Time (h)	Workup[a]	Yield (%)[b]
1	0.03	10	$Me(EtO)_2SiH$ (2.4) PMHS (8)	20.5	A	80
2	0.03	10	PMHS (8)	17	B	50
3	0.05	10	PMHS (8)	14.5	A+B	24[c]
4	0.05	10	$Me(EtO)_2SiH$ (3)	4.5	A[d]	79
5	0.10	10	Ph_2SiH_2 (1.5+0.5)	19	A[d]	60
6	0.05	10	$Me(EtO)_2SiH$ (3+3) PMHS (1)	4	A[d]	16[c]
7	0.05	10	$Me(EtO)_2SiH$ (3)	15	B+C	70
8	0.05	5	$Me(EtO)_2SiH$ (3)	16	C	90
9	0.24	5	$Me(EtO)_2SiH$ (3)	4	C	83
10	0.26	5	$Me(EtO)_2SiH$ (3)	4.5	C	88
11	1.52	5	$Me(EtO)_2SiH$ (3)	2	C	84

a) Workup methods: A) 1.5 equiv TBAF. B) aq. $NaHCO_3$. C) 5 equiv AcOH, 1.5 equiv TBAF. b) Isolated yield. c) Extensive overreduction observed. Alcohols isolated in 1:3 *syn:anti*-ratio. d) C2 epimerization of **72** observed.

2.4 Selective ketone reductions

The final stereocenter in amaminol A **1** required a diastereoselective reduction where amino acid-based chirality at C2 is directing the hydride addition. Although similar reductions were found in the literature,[48] it seemed that there is no general solution to the problem. The outcome of the reduction can be predicted using the Felkin-Ahn model. There are three possible conformers **A**-**C** that might occur when the reaction takes place (Figure 4). Conformers **A** and **B** follow the Felkin-Ahn model and conformer **C** is a model of chelation control. Only the conformer **A** leads to the desired *syn*-stereochemistry present in amaminol A **1**. Fortunately, this conformer is generally predominant. Methyl group is a small functionality, which plausibly directs the

transition state conformers **B** and **C** towards the undesired *anti*-stereochemistry. If chelation control is operational, the major conformer is **C**, which also leads to the *anti*-isomer.

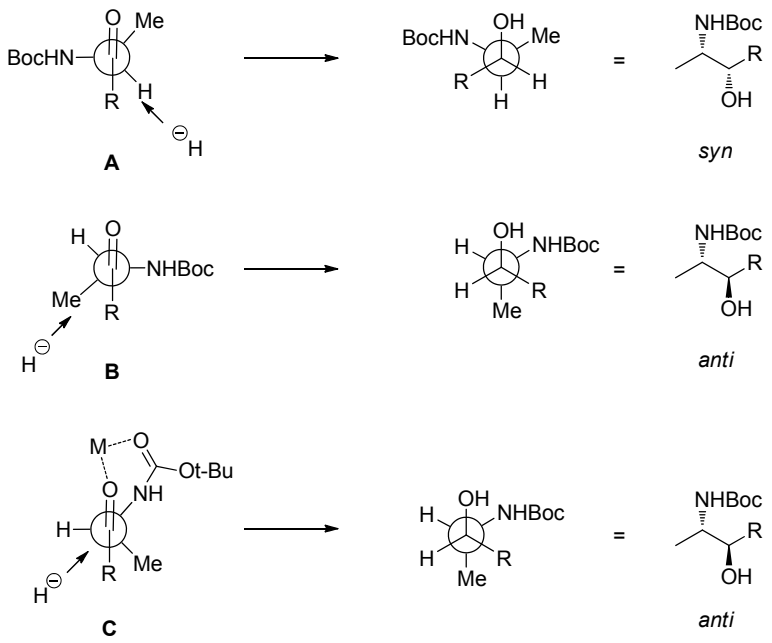
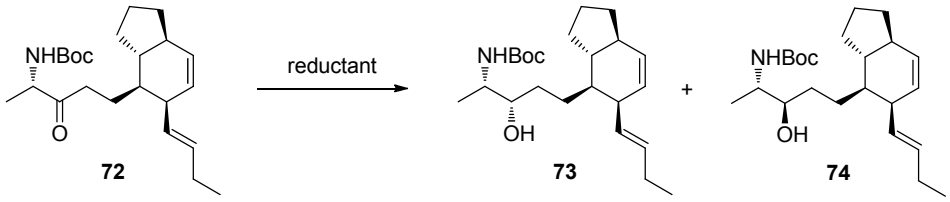


Figure 4. The Felkin-Ahn model leading to *syn*- and *anti*-isomers.

A variety of reductants were tested (Table 3). Highly bulky Li(*t*-BuO)$_3$AlH gave an approximately 3:1 *syn*-selective reaction (entry 1).[48c] Cooling the reaction temperature down to -78 °C reduces the selectivity to 3:2 (*syn:anti*), since the solubility of the reductant into THF decreases (entry 2). The bulky chiral reductant (*S*)-Alpine hydride also gave the *syn*-product **73** as the major component, but the product was contaminated with reductant-based impurities, and thus the purification was challenging (entry 3).[48d-e] DIBAL-H gave almost equal amounts of both isomers (entries 4-5). Other boron reductants were *anti*-selective giving 1:2-1:3 (*syn:anti*)-ratios (entries 6-8). The best *anti*-selectivity was observed when bulky Li(*t*-BuO)$_3$AlH was used in ethanol (entry 9).[48c] From these results we can conclude that the final reduction step for amaminols A **1** and B **2** can be performed by using Li(*t*-BuO)$_3$AlH in THF or ethanol, respectively. Fortunately, isomers **73** and **74** were separable in silica gel chromatography. Both isomers were also found to be crystalline and can be further purified by recrystallization.

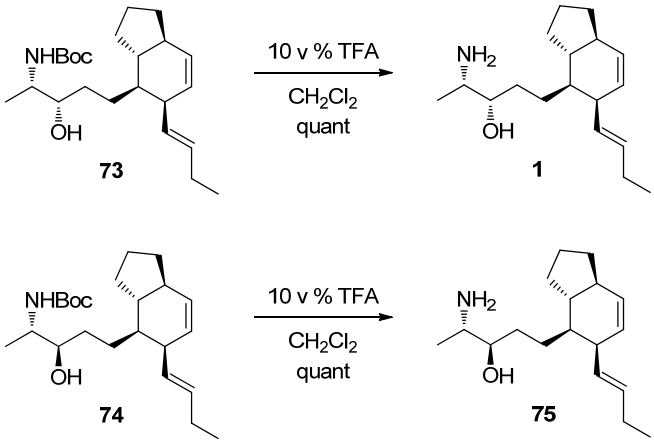
Table 3. Diastereoselective reduction of α-chiral ketone **72**.



Entry	Reductant	Conditions	*syn:anti*[a]	Yield (%)
1	Li(*t*-BuO)$_3$AlH	THF, -30 °C	76:24	97
2	Li(*t*-BuO)$_3$AlH	THF, -78 °C	58:42	99
3	(*S*)-Alpine hydride	THF, -78 °C	71:29	75[b]
4	DIBAL-H	THF, -78 °C	42:58	98
5	$ZnBr_2$, DIBAL-H	THF, -78 °C	42:58	50
6	L-Selectride	THF, -78 °C	30:70	89
7	$KBEt_3H$	THF, -78 °C	29:71	74
8	$CeCl_3$•$7H_2O$, $NaBH_4$	MeOH, 0 °C	24:76	99
9	Li(*t*-BuO)$_3$AlH	EtOH, -78 °C	19:81	99

a) Determined from ^{1}H-NMR data. b) Major contamination of the product by reductant impurities.

Finally Boc-protection was removed with trifluoroacetic acid to give amaminol A **1** and *epi*-amaminol A **75** after aqueous basic workup. Unfortunately we could not initially match the spectra of either product with those of the isolated natural products.



Scheme 14. Finalization of amaminol A **1** and *epi*-amaminol A **75** synthesis.

2.5 Structural evaluation of amaminol A

The failure in matching the spectral data of our synthetic amaminol A **1** to the natural one led us to a careful structural analysis of the synthesis intermediates and precursors. The C6 stereocenter of enone **70** was confirmed with selective 1D COSY NMR analysis due to high risk of epimerization in HWE-reaction. Coupling constants between H5-H6 and to H6-H7 were found to be 10.5 Hz, which was taken as an indication of axial-axial couplings (Figure 5). The coupling constant between H6-H14 was 6.2 Hz, suggesting axial-equatorial coupling. These findings confirmed that no epimerization had occurred, and we still had the correct stereochemistry.

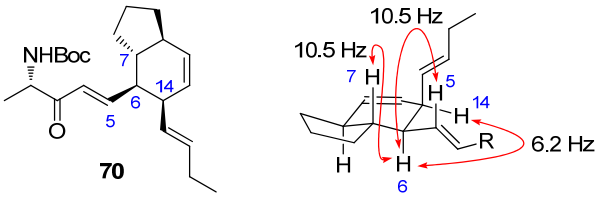
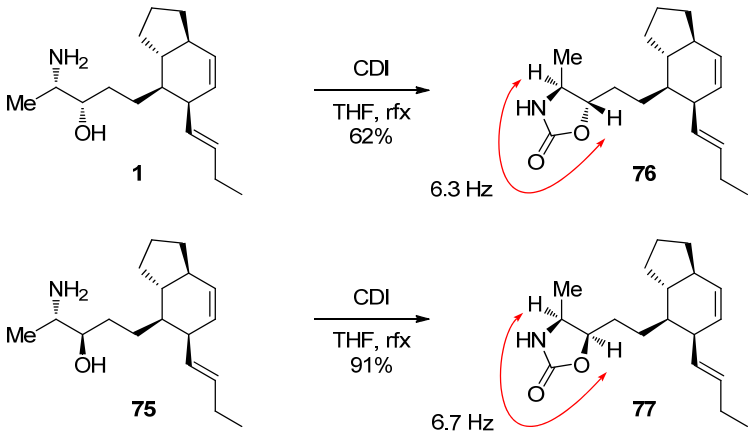


Figure 5. Structural evaluation of enone **70**.

The final ketone reduction led to two different isomers. In order to distinguish which isomer was (*2S,3S*) and which was (*2S,3R*), we transformed both amino alcohols **1** and **75** into their corresponding cyclic carbamates **76** and **77** with carbonyl diimidazole (CDI) (Scheme 15). Coupling constants between H2-H3 were and 6.3 Hz (for **76**) and 6.7 Hz (for **77**), and therefore we could not rely on this data for accurate determination of the relative stereochemistry.



Scheme 15. Transformation of amaminol A **1** and *epi*-amaminol A **75** to carbamates.

However, NOE experiments combined with molecular modeling (Hyperchem software v. 7.51 with MM+ theory) suggested the stereochemical assignments to be *2S,3S* for **76** and *2S,3R* for **77** (Figure 6).

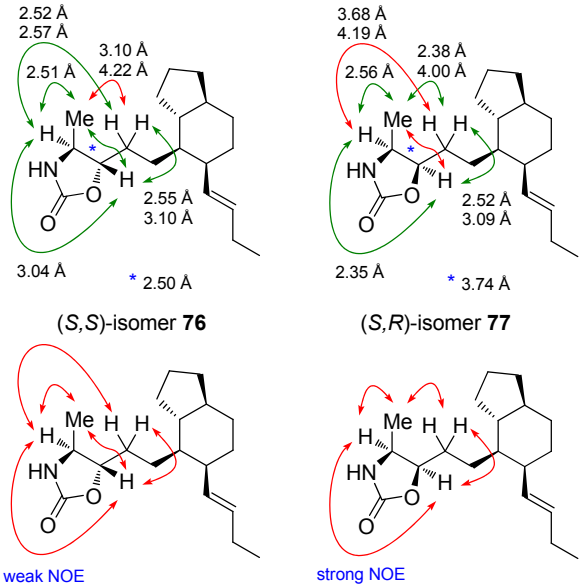


Figure 6. NOE-study of absolute stereochemistries of **76** and **77**. Measured distances from molecular modeling are shown on top and observed NOE's are presented at the bottom.

Luckily we were able to crystallize carbamate **76** to obtain its crystal structure and verify the absolute stereochemistry (Figure 7). The stereochemistry matched those reported for amaminol A **1**.

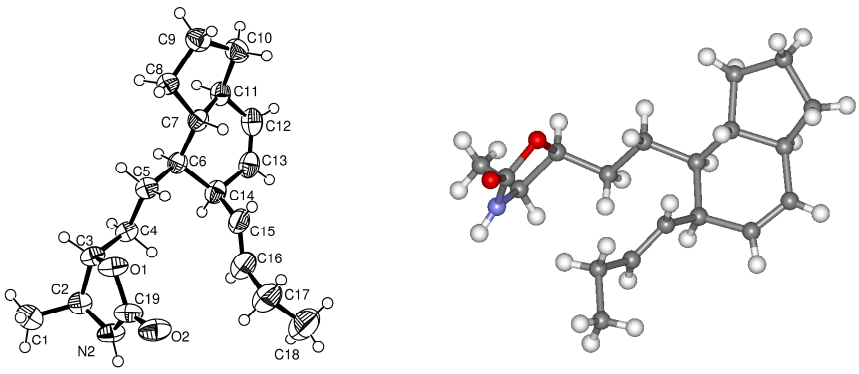


Figure 7. A plot of the X-ray crystal structure of carbamate **76** with atom labels and thermal displacement parameters at 50% probability level.

At this point we obtained NMR data for the isolated *N*-Boc protected amaminol A **73** and its derivative cyclic carbamate **76**. Spectal data of these compounds matched those of our synthetic material. We still could not match the spectra of our synthetic amaminol A **1** to the originally reported spectra, but all other data confirmed that we had the correct compound. Careful examination of the original isolation procedure revealed that the reported data are most likely for the corresponding trifluoroacetic acid salts of natural amaminols.[1] Accordingly, after conversion of synthetic **1** into its corresponding TFA salt, the NMR spectra of the synthetic and the natural product matched.

2.6 Biologigal activity of amaminol A

Biological activity of amaminol A **1** was tested at National Cancer Institute (NCI) against multiple different cancer cell lines. Originally isolated amaminols were tested to have cytotoxic activity against P_{388} murine leukaemia cells with an IC_{50} value of 2.1 μg/mL. Our discovery that amaminols were isolated as their corresponding TFA salts has an influence on previously measured biological data. If TFA is taken into account in the calculation of molecular mass, the original data correspond to an IC_{50} inhibition value of 5.3 μM. Research done at NCI revealed that amaminol A **1** has cytotoxic activity against variety of cancer cell lines. Generally GI_{50} (same as IC_{50}) values were between 1-10 μM (Figures 8-9). The most consistent activities were found against colon cancer, central nervous system (CNS) cancer, melanoma and ovarian cancer cell lines.

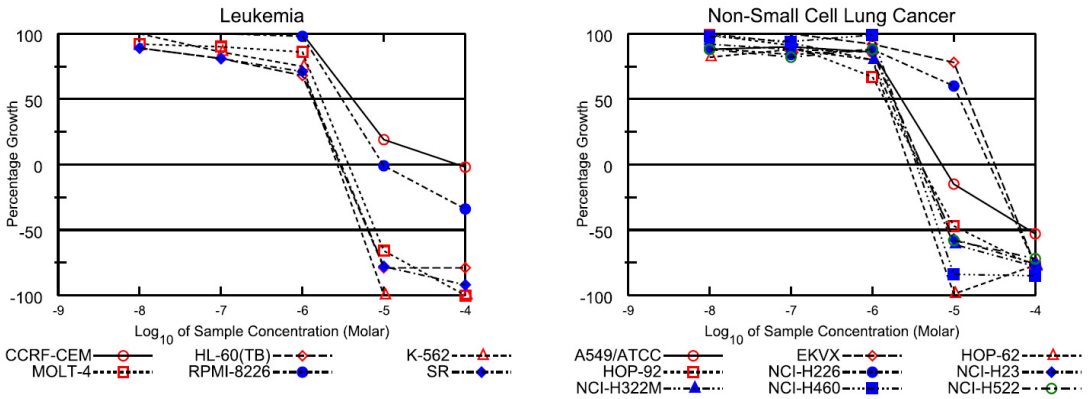


Figure 8. Cytotoxic activity against leukaemia and lung cancer.

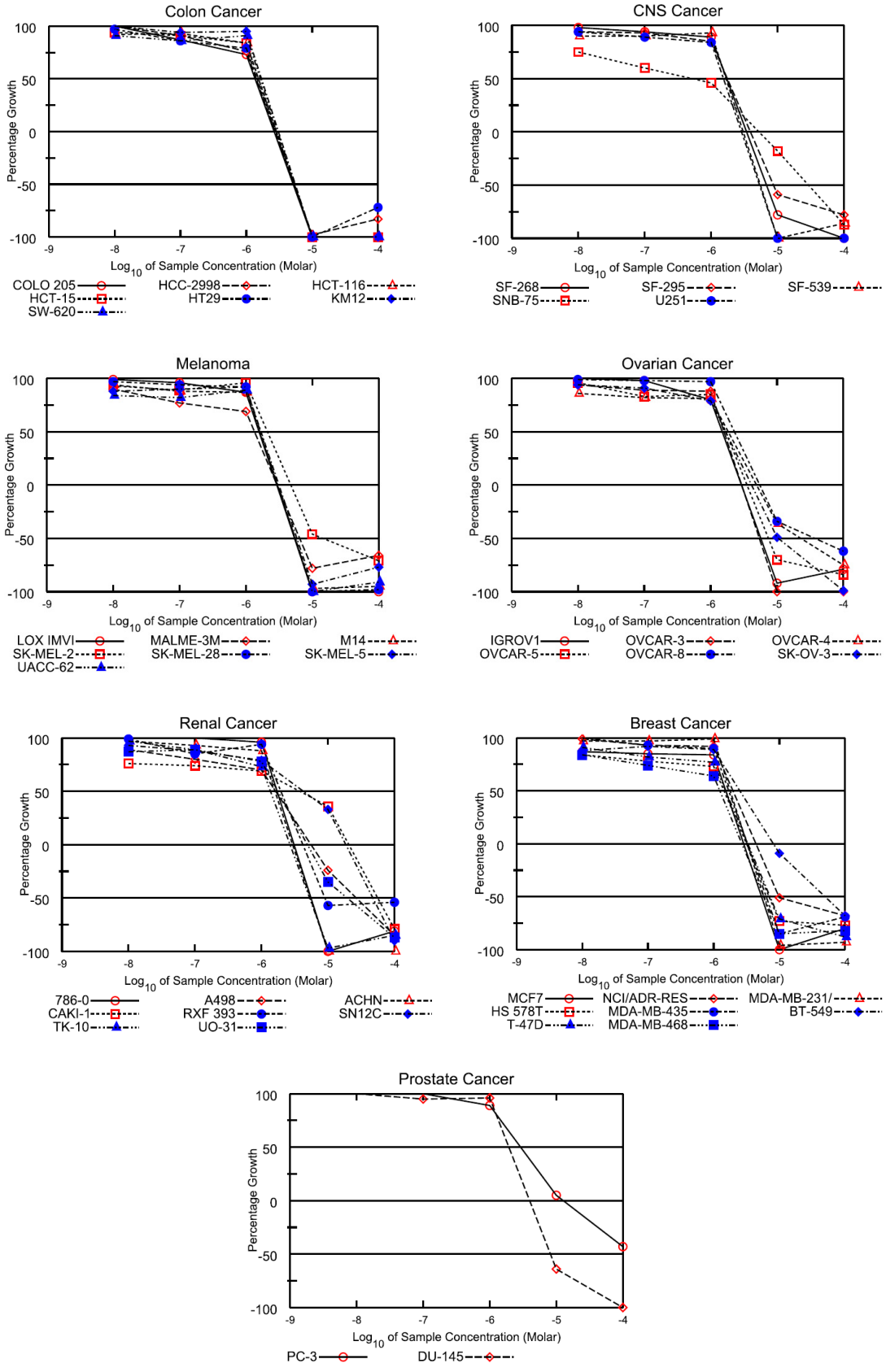


Figure 9. Cytotoxic activity against variety of cancer cell lines.

3 ACHIRAL COPPER HYDRIDES IN 1,4-REDUCTIONS

Early results in the use of copper hydride obtained during the total synthesis of amaminol A **1** (Table 2) led us to explore these reactions further. At the time it seemed that major development efforts were focused on enantioselective reactions. Also, the existing reviews mostly focused on the use of the readily available Stryker's reagent or *in situ* generated copper hydride catalyst in asymmetric reactions.[49,50] Practical procedures for non-asymmetric catalytic *in situ* generated copper hydride reactions were extremely hard to find.

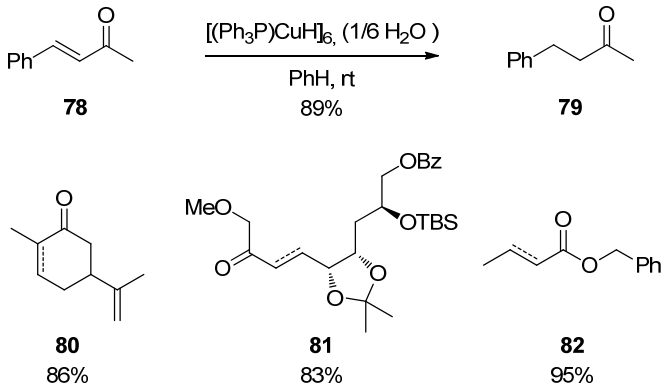
3.1 Conjugate reduction with stoichiometric Stryker's reagent

The history of copper hydrides dates back to 1844, when Würtz generated copper hydride species by treating aqueous copper(II) sulfate with hypophosphorous acid.[51,52] The resulting red-brown, thermally unstable pyrophoric material was identified to have the approximate composition of CuH. Ligand-stabilized copper complexes were not known until 1952, when Wiberg and Henle generated "CuH" from CuI and $LiAlH_4$ in pyridine-ether solvent.[53] Copper hydride generated in this way was fully soluble in pyridine and could be isolated by precipitation with ether.[54] Material produced in this way was thermally unstable and decomposed partially at room temperature and fully at 60 °C. Soluble forms of this "CuH" in pyridine decomposed already above -20 °C.

Probably the first thermally stable crystalline phosphine-stabilized copper hydride complexes [$CuH{\bullet}2P(OEt)_3$ and $CuH{\bullet}3PPh_3$] were reported by Malykhina and co-workers in 1967.[55] A study on copper hydrides stabilized by phosphines was reported by Dilts and Shiver in 1969.[56] They estimated the number of ligands around copper with cryoscopic titration of the readily made solution of "CuH" in pyridine with PBu_3, PEt_2Ph, $PBuPh_2$, PPh_3, $S{=}PPh_3$, $P(OMe_3)_3$, $P(OCH_2)_3CMe$ and dppe. They could not isolate any of the "CuH"-phosphine complexes and were also unable to reproduce the results from Malykhina since no experimental procedures were given. In their following

paper in 1971, Malykhina *et al.* described the multigram synthesis of the crystalline complex CuH•P(*i*-OPr)$_3$ derived from CuCl, *iso*-propylphosphite and Et_3SnH, and complexes 3CuH•2P(*i*-OPr)$_3$ and CuH•3P(NMe$_2$)$_3$ derived from isolated CuH and the appropriate phosphorous compound.[57] Whitesides *et al.* studied some organometallic reactivity of stabilized copper hydrides in 1969 by complexing "CuH" with PBu_3.[58] They generated their copper hydride from the reaction of CuBr with DIBAL-H in pyridine.

A major leap forward was made when the thermally stable copper hydride cluster [(PPh$_3$)CuH]$_6$•DMF was reported by Churchill and co-workers in 1971.[59] This complex was not of interest to the general scientific community, until Stryker and co-workers reported the use of stoichiometric amounts of [(PPh$_3$)CuH]$_6$ for the highly chemoselective reduction of α,β-unsaturated enones and esters in 1988 (Scheme 16).[44] This new methodology was adopted by synthetic chemists and has been widely used, as shown in this chapter. The complex [(PPh$_3$)CuH]$_6$ was later named "Stryker's reagent" and it eventually became commercially available.

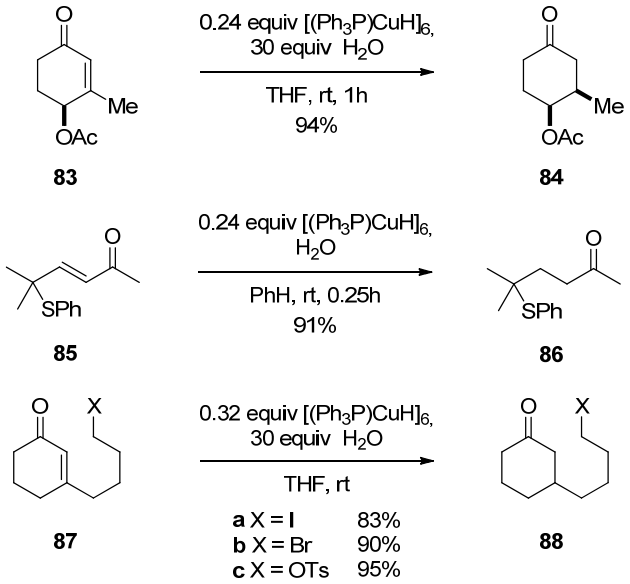


Scheme 16. Original Stryker's conjugate reduction conditions.[44]

3.1.1 Stryker's reagent in the reduction of enones

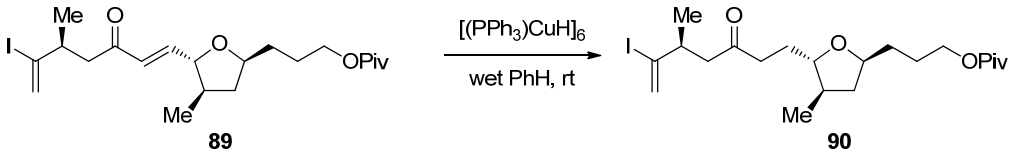
In 1990 Stryker and co-workers reported a study on the chemoselectivity of [(PPh$_3$)CuH]$_6$.[60] They reported that the enone **83** was selectively reduced to the ketone **84** in high yield and selectivity (Scheme 17). They did not observe elimination of the acetate group, which is known to eliminate when treated with Me_2CuLi. They also were able to reduce the thioether-containing enone **85**, which was expected to be sensitive to radical character. Sensitivity of different leaving groups was tested when enones **87a-c**

were reduced to ketones **88a-c**. Halogens or tosylate were not affected by these conditions and high yields of isolated product were obtained. If the reduction of **87a** was conducted under anhydrous conditions, partial reductive cyclization was observed.



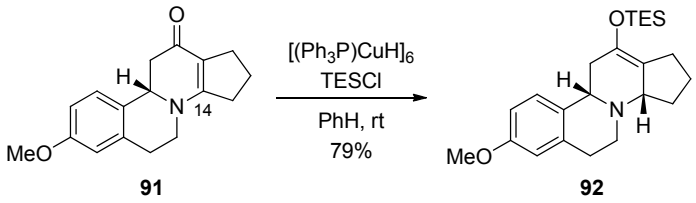
Scheme 17. Stryker's study on the chemoselectivity of $[(PPh_3)CuH]_6$.[60]

In 1992 Kishi and co-workers reported the total syntheses of halichondrin B and norhalichondrin B.[61] They received a sample of $[(PPh_3)CuH]_6$ from Stryker which was used to reduce enone **89** to the corresponding ketone **90** with no double bond isomerisation taking place (Scheme 18). The outcome of this reaction is difficult to estimate since no comments or yield was given.



Scheme 18. Early example of the use of Stryker's reagent in total synthesis.[61]

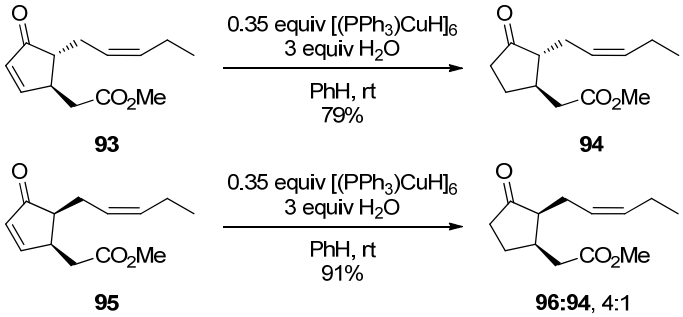
Myers and Elworthy chose to use Stryker's original method in the reduction of a conjugated enone on a bicyclic core in the synthesis of azasteroids (Scheme 19).[62] The corresponding copper enolate was trapped with triethylsilyl chloride (TESCl) to give the silyl enolate **92**, which was found to be stable enough to be purified with silica gel chromatography. The reduction was also found to be highly diastereoselective since only 3% of the undesired isomer was found on the newly generated stereocenter at C14.



91 **92**

Scheme 19. Stryker's reagent in the formation of silyl enol ether in the synthesis of (-)-8-Azaestrone.[62]

Bestmann and co-workers used Stryker's reagent in the synthesis of (-)-methyl jasmonate **94** and (+)-*epi*-methyl jasmonate **96**, the fragrance constituents of jasmine oil (Scheme 20).[63] Selective reduction was the last operation in both of these total syntheses. Unfortunately, the *cis*-isomer **96** was found to epimerize in the process. They concluded that epimerization was the result of chromatography and not the actual reaction procedure.

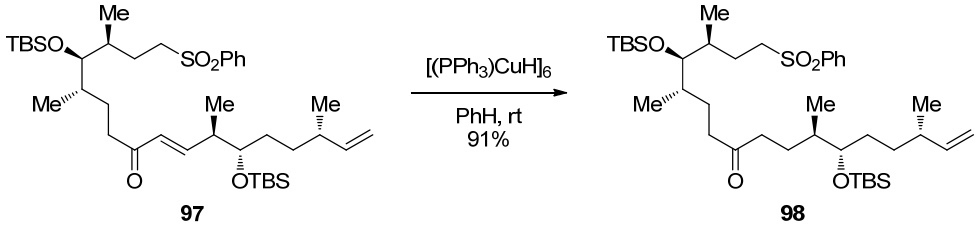


93 **94**

95 **96:94**, 4:1

Scheme 20. Stryker's reagent in the synthesis of fragrances of jasmine oil.[63]

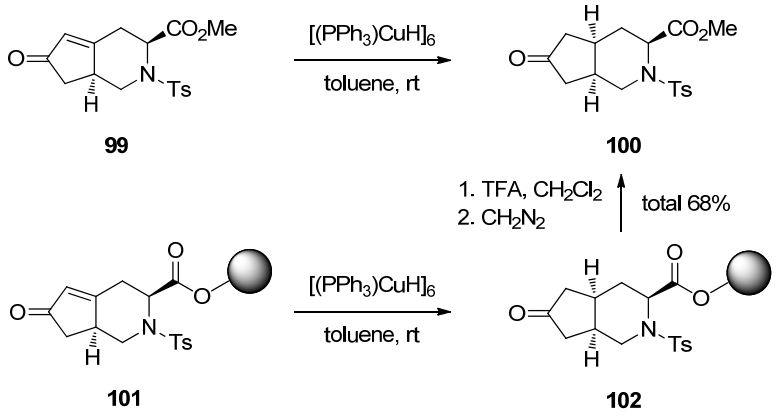
In 1997 Isobe and co-workers constructed the tautomycin segment C by using Stryker's reagent in the reduction of a key enone **97** in high yield (Scheme 21).[64] The isolated terminal double bond and phenyl sulfone both tolerated these reaction conditions and were not reduced in the process.



97 **98**

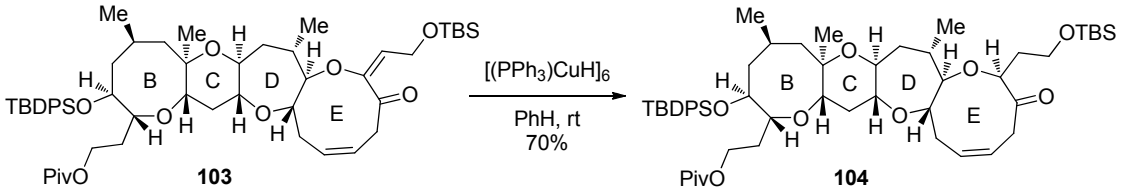
Scheme 21. Enone reduction in the synthesis of the tautomycin fragment C.[64]

The first example of the use of Stryker's reagent in solid phase synthesis was reported by Bolton *et al.* in 1997 (Scheme 22).[65] They were looking for a reduction method, which would be fully functional in both solution phase and solid phase. After a survey of multiple methods, the commercial Stryker's reagent proved to be the most functional reductant giving good yields. They also noted that commercial Stryker's reagent is very sensitive to air, and the best outcomes were obtained with freshly opened bottles of commercial copper hydride.



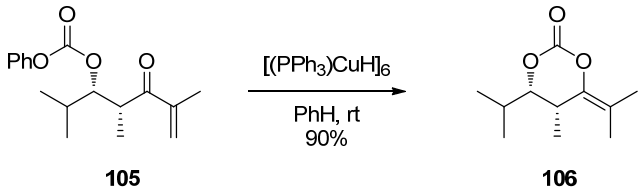
Scheme 22. Copper reduction on Wang resin supported substrate.[65]

A very remarkable example of the use of copper hydrides was reported in 1999 by Nicolaou *et al.* in the first total synthesis of brevetoxin A.[66] They used Stryker's reagent in the reduction of an *exo*-cyclic α,ß-unsaturated ketone in a 9-membered ring (Scheme 23). This enone was also a part of an enol ether substructure, which made the transformation more challenging. The workup gave the desired isomer of the α-chiral ketone **104**. It it also noteworthy that the *Z*-double bond in the E-ring was not isomerized, since both acidic and basic conditions could have led to the formation of the energetically more favoured enone.



Scheme 23. Stryker's reagent in the total synthesis of Brevetoxin A.[66]

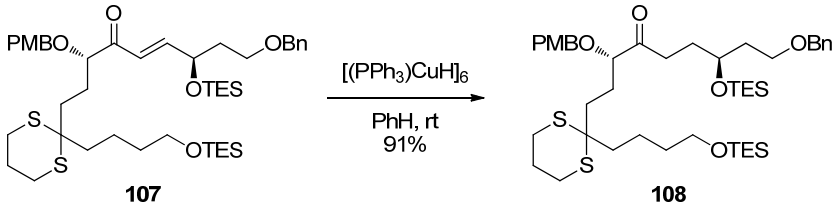
Raimundo and Heathcock demonstrated the use of copper hydride in the generation of a cyclic 6-membered carbonate in the C7-C13 model compound for lankamycin.[67] Enone **105**, containing an acyclic carbonate, was reduced with Stryker's reagent (Scheme 24). The corresponding copper enolate reacted directly with the carbonate moiety, forming the cyclic carbonate **106** in excellent yield.



105 **106**

Scheme 24. Stryker's reagent in the formation of a cyclic carbonate.[67]

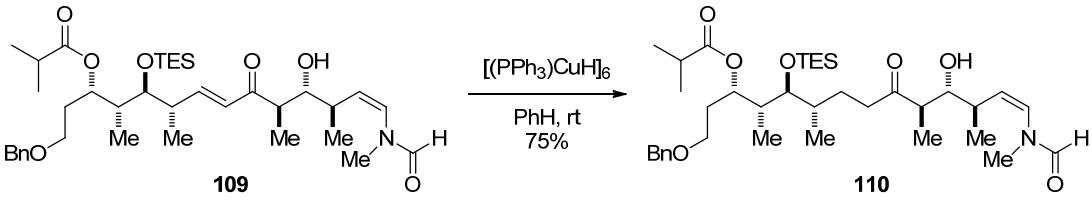
Hashimoto and co-workers used Stryker's reagent in the synthesis of C10-C31 (BCDEF ring) portion of pinnatoxin A.[68] Among the many methods tested, Stryker's reagent was found to be the optimal choice for selective reduction. Enone **107** was selectively reduced to the corresponding ketone **108** in high yield (Scheme 25



107 **108**

Scheme 25. Stryker's reagent in pinnatoxin synthesis.[68]

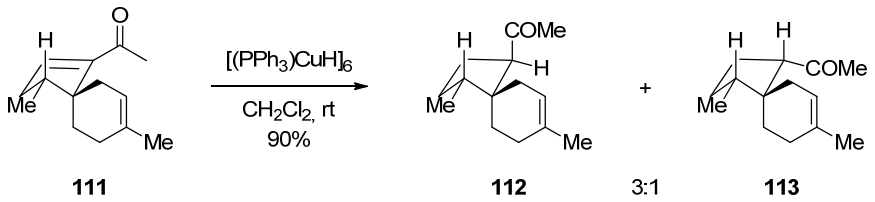
Paterson and co-workers have demonstrated the use of copper hydrides on multiple occasions in total syntheses of complex natural products. They used Stryker's reagent in the synthesis of a C21–C34 subunit of aplyronines by reducing enone **109** to the corresponding ketone **110** in the presence of a vulnerable *Z*-enamide and an unprotected hydroxyl functionality (Scheme 26).[69]



109 **110**

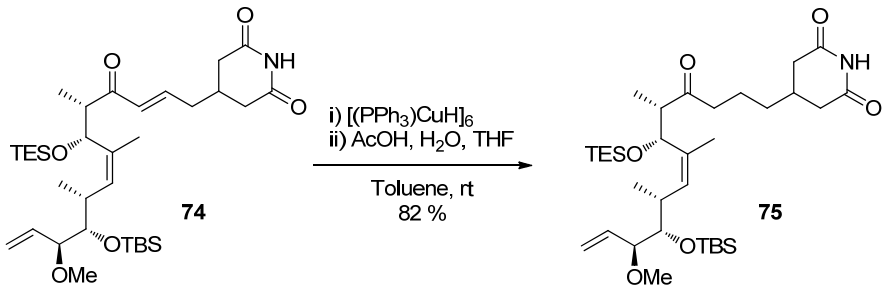
Scheme 26. Stryker's reagent in the synthesis of a subunit of aplyronines.[69]

In 2003 Tamiya and Sorensen used Stryker's reagent for the reduction of a bicyclic enone **111** in the synthetic studies towards (-)-hispidospermidin (Scheme 27).[70] Although the conjugate reduction worked well and gave a high combined yield of ketones **112** and **113**, the undesired isomer **112** was the major product. Any attempts to epimerize this to the desired isomer **113** failed, and they changed their synthesis route. Most interestingly, they performed this reaction in dichloromethane instead of benzene or toluene as reported by other groups.



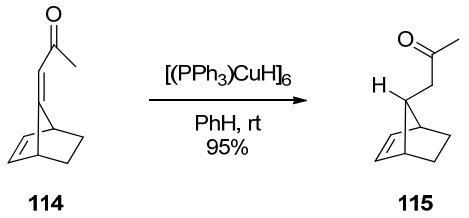
Scheme 27. Undesired stereochemical outcome in (-)-hispidospermidin synthesis.[70]

As we reported in section 2.3 (Scheme 13), the most interesting example of the usage of Stryker's reagent was reported by Danishefsky and co-workers in 2003-2004.[43] In their synthesis of (+)-migrastatin they selectively reduced the enone **74** to the corresponding ketone **75** in the presence of a terminal olefin, a *Z*-olefin, and most importantly, a slightly acidic NH-proton (Scheme 28). This was the first instance in copper hydride reductions, where the substrate had free NH-protons. We used these observations in our early developments of copper hydride-catalyzed conjugate reductions (Table 2).



Scheme 28. Conjugate reduction from Danishefsky and co-workers in the synthesis of (+)-migrastatin.[43]

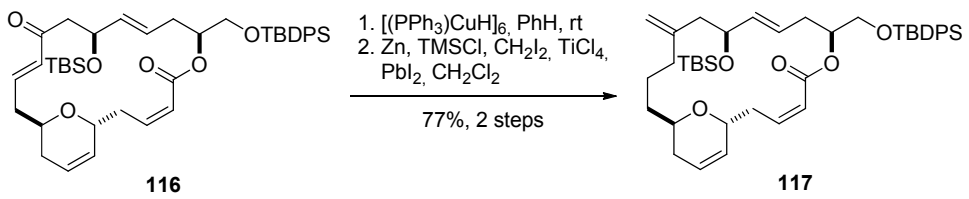
In 2004 Holtsclaw and Koreeda reported a conjugate reduction of an enone **114** containing a bicyclic core (Scheme 29).[71] Reduction occurred from the less hindered side of the enone, where the other isolated double bond in the ring structure reduced the steric hindrance.



114 **115**

Scheme 29. Facially selective conjugate reduction of hindered bicyclic enone.

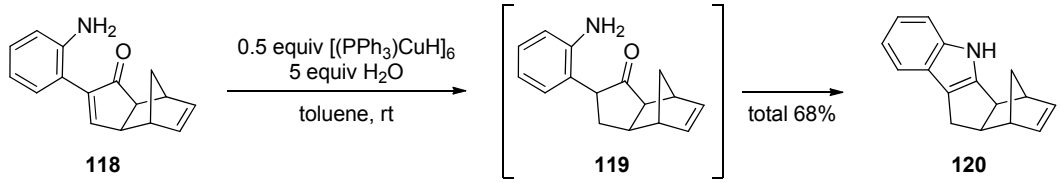
In 2004 Paterson and co-workers used Stryker's reagent in the synthesis of laulimalide analogues.[72] They were able to selectively reduce an enone in the presence of an α,β-unsaturated ester and other isolated double bonds (Scheme 30). The resulting ketone was then olefinated using Takai methylenation giving a good combined yield of 77%.



116 **117**

Scheme 30. Enone reduction in the synthesis of laulimalide analogues.[72]

Coogan *et al.* have constructed structurally strained indoles *via* aniline-containing enones.[73] They observed that enone **118** did not close the ring by forming an imine, since the system was either too strained, or the enone was not reactive enough (Scheme 31). When the enone was selectively reduced with Stryker's reagent, they observed spontaneous ring closure to the corresponding indole **120**. Interestingly, free anilinic NH-protons did not influence the reactivity of Stryker's reagent.

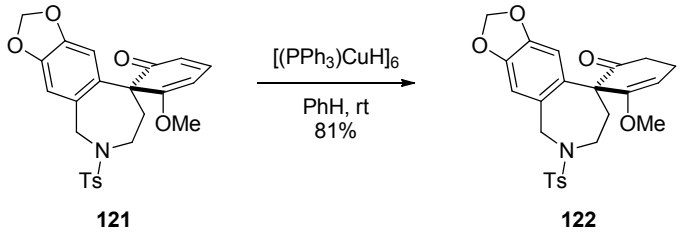


118 **119** **120**

Scheme 31. The use of Stryker's reagent in spontaneous cyclization.[73]

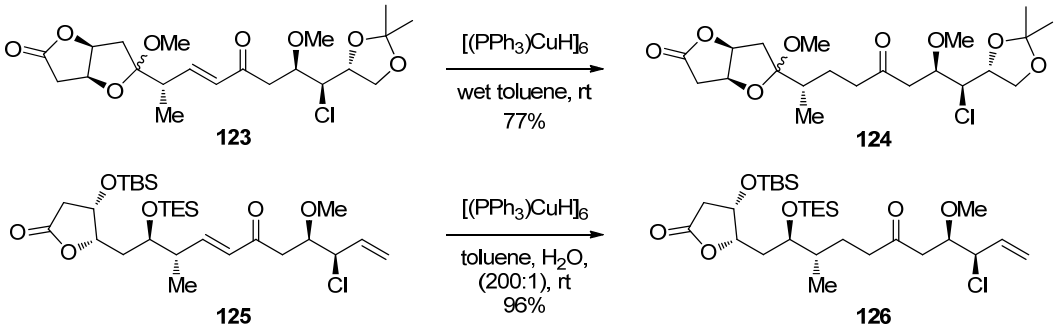
Moon *et al.* reported the synthesis of cripowelling skeleton *via* an oxidative C-C bond forming reaction, resulting in the bicyclic intermediate **121**.[74] This dienone was highly unstable and decomposed under various conditions including catalytic hydrogenation

with PtO_2. They chose to reduce the α,β-double bond of the dienone **121** with Stryker's reagent and obtained the corresponding enolate **122** in a high 81% yield.



Scheme 32. Stryker's reagent in a challenging dienone reduction.[74]

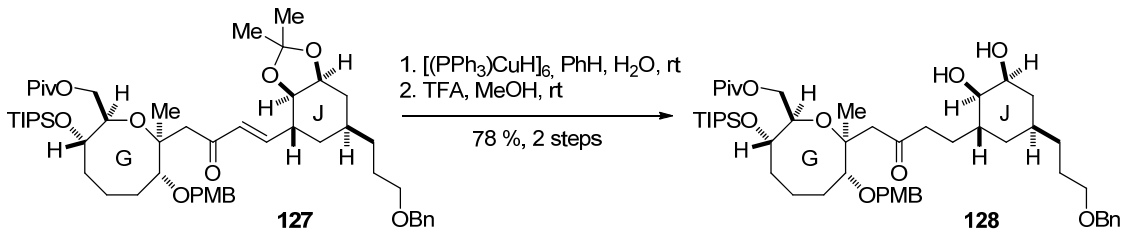
In 2005 Paterson *et al.* described the challenging 1,4-reduction of an enone **123** in the presence of a variety of vulnerable functionalities such as a lactone, acetals, chloride and an easily eliminating β-methoxy group relative to ketone (Scheme 33).[75a] Their initial trials with palladium led to decomposition. The problem was eventually solved by conducting this reduction with Stryker's reagent. They observed that wet toluene compared to dry conditions accelerated the reaction and required smaller quantities of the reagent. Later the Paterson group changed their approach slightly.[75b] In the new system, the reduction of the enone **125** with Stryker's reagent was conducted in the presence of an allylic chloride, which was not affected by these reductive conditions. Once again, Stryker's reagent proved to be a highly selective reductant under mild conditions.



Scheme 33. Stryker's reagent in the synthesis of DEF subunit of spirastrellolide A.[75]

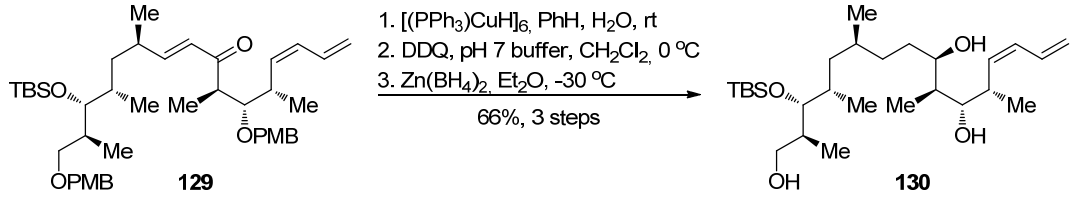
Crimmins *et al.* reported the use of Stryker's reagent in the synthesis of the GHIJ subunit of brevetoxin A in 2006.[76] They reduced the enone **127** to the corresponding ketone in the presence of protecting groups otherwise vulnerable to reductive

conditions, such as PMB and Bn (Scheme 34). Acetonide was then removed with trifluoroacetic acid to give the ketone **128** in a good combined yield of 78%.

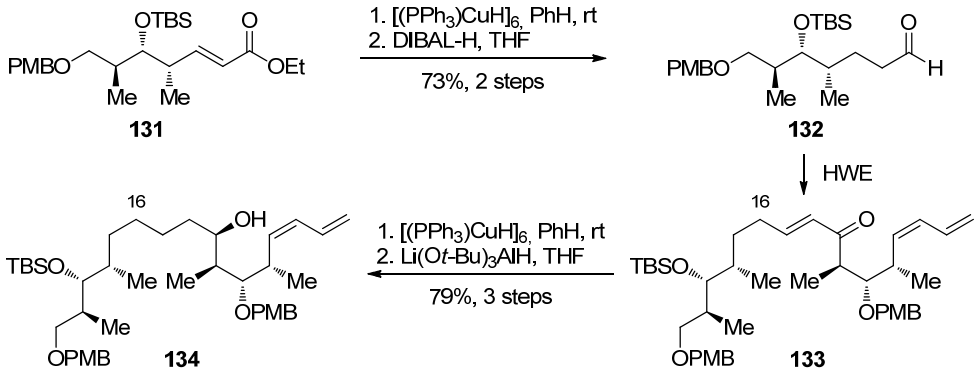


Scheme 34. Copper reduction in the synthesis of GHIJ Fragment of Brevetoxin A.[76]

Synthesis of (-)-dictyostatin and its analogues has proven to be an excellent target to demonstrate the utility of Stryker's reagent. In 2004 Paterson *et al.* reported the use of Stryker's reagent in the first total synthesis of (-)-dictyostatin.[77] They selectively reduced the enone **129** in the presence of *p*-methoxybenzyl protections and a terminal diene substructure (Scheme 36). Later they also expanded the use of Stryker's reagent in the earlier stages of the synthesis by reducing an α,β-unsaturated ester **131** when constructing the (-)-dictyostatin analogue 16-desmethyl-dictyostatin (Scheme 36).[78]

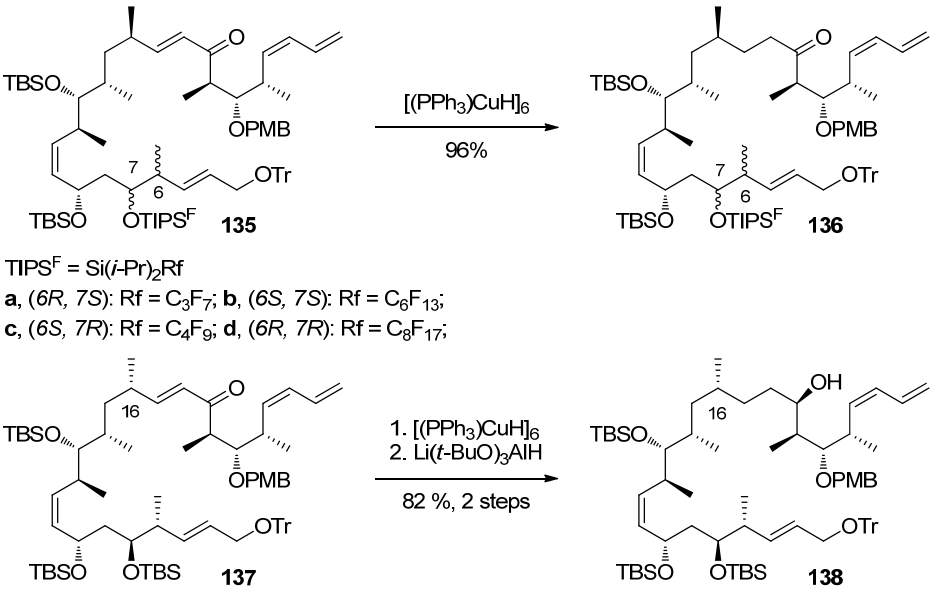


Scheme 35. Stryker's reagent in the total synthesis of (-)-dictyostatin.[77]



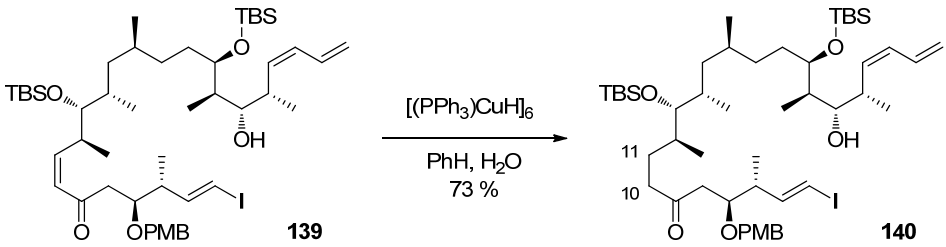
Scheme 36. Stryker's reagent in the total synthesis of dictyostatin analogue 16-desmethyl-dictyostatin.[78]

Curran and co-workers were also working on a total synthesis of (-)-dictyostatin in 2006.[79] In order to establish the correct stereochemistry at C6 and C7, they tagged different isomers with fluorous protective groups and conducted the synthesis of four isomers of dictyostatin (Scheme 37). Curran and co-workers chose to use the same conjugate reduction conditions demonstrated earlier by the Paterson group. Reduction of enone **135** with Stryker's reagent gave the ketone **136** in excellent yield without affecting the isolated double bonds or protective groups. They also used this approach when synthesizing an 16-*epi*-dictyostatin analogue.[80]



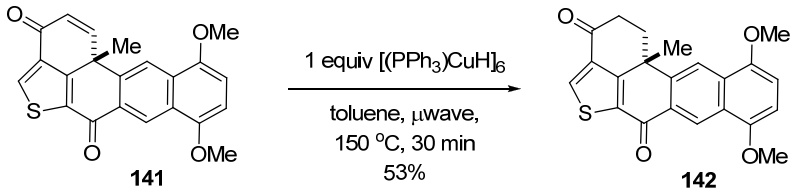
Scheme 37. Stryker's reagent in the synthesis of (-)-dictyostatin[79] and 16-*epi*-dictyostatin.[80]

Paterson *et al.* synthesized a series of (-)-dictyostatin analogues in 2008.[81] They and the Curran group have both demonstrated the utility of Stryker's reagent in earlier stages of the synthesis. In this recent study, Paterson and co-workers removed a double bond at C10-C11 with Stryker's reagent in the synthesis of 10,11-dihydrodictyostatin (Scheme 38).



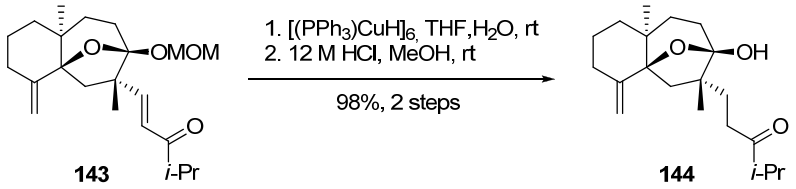
Scheme 38. Stryker's reagent in the synthesis of 10,11-dihydrodictyostatin.[81]

Wipf and co-workers reported a microwave-assisted enone reduction with Stryker's reagent in 2007 (Scheme 39).[82] They performed the reaction at 150 °C, which is rather surprising. Stryker's reagent is reported to be thermally stable with a melting point of 111 °C.[59] Other copper hydride species are less stable and decompose easily. Wipf and co-workers did not comment on the selection of such harsh reaction conditions, but they were able to reduce enone **141** to the corresponding ketone **142** in moderate yield.



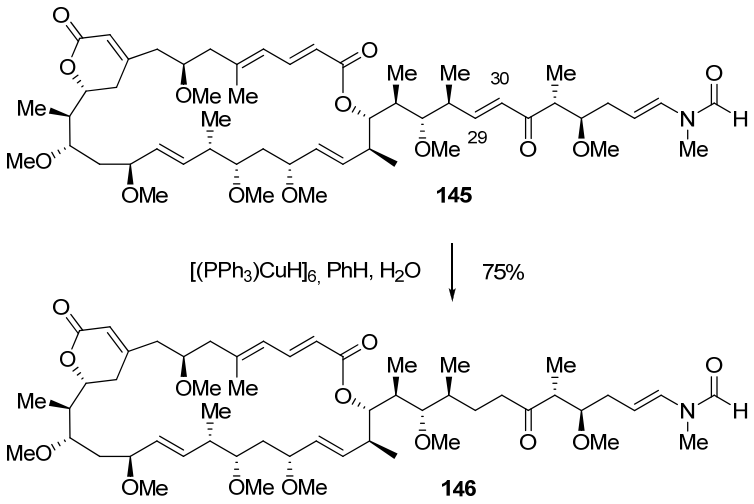
Scheme 39. Conjugate reduction under microwave irradiation in the synthesis of (±)-Thiohalenaquinone.[82]

Lam and Chiu reported the use of Stryker's reagent at late stages of the total synthesis of (-)-indicol **144** (Scheme 40).[83] They reduced enone **143** to the corresponding ketone in the presence of an isolated exocyclic terminal double bond and an acetal functionality. After removal of the MOM-protection, they obtained (-)-indicol **144** in a nearly quantitative yield.



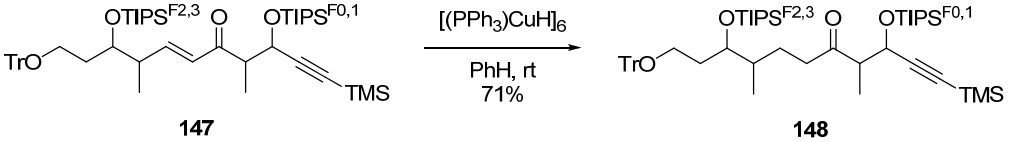
Scheme 40. Copper reduction in the total synthesis of (-)-indicol **144**.[83]

Paterson *et al.* reported an example of the use of copper hydrides in 2007.[84] Their previous knowledge on the selectivity of Stryker's reagent led them to use this methodology in the last step of a total synthesis of (-)-reidispongiolide A **146** (Scheme 41). They were able to reduce an α,β-unsaturated ketone **145** at C29-C30 in the presence of an α,β-unsaturated lactone, an α,δ-unsaturated macrolactone, an *E*-enamide and other isolated double bonds. Taking the difficulty of the task into consideration, (-)-reidispongiolide A **146** was obtained in an excellent 75% yield.



Scheme 41. Stryker's reagent in the total synthesis of (-)-reidispongiolide A **146**.[84]

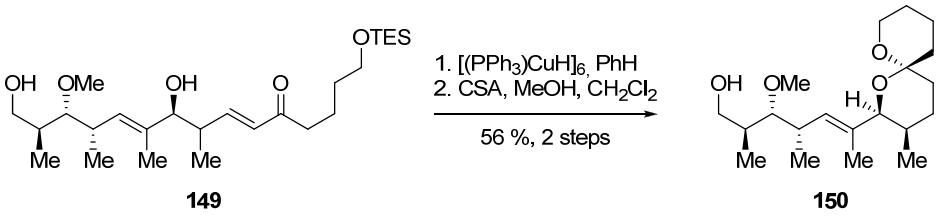
Curran and co-workers constructed four different isomers of cytostatin using fluorous mixture synthesis.[85] One of the key steps was the reduction of an enone by Stryker's reagent (Scheme 42). Enone **147** contained a triple bond substructure, which was not affected by this reductive transformation. This observation is surprising, since Stryker and co-workers have reported that triple bonds undergo reductive hydrocupration with $[(PPh_3)CuH]_6$.[86] It is possible that the TMS-group influences the reactivity by causing steric hindrance or changing the electronic nature of the π-system, therefore inhibiting the reduction.



$TIPS^{F0}$ = Si(*i*-Pr)$_3$ (zero fluorine); $TIPS^{F1}$ = Si(*i*-Pr)$_2$$CH_2CH_2C_4F_9$;
$TIPS^{F2}$ = Si(*i*-Pr)$_2$$CH_2CH_2C_6F_{13}$; $TIPS^{F3}$ = Si(*i*-Pr)$_2$$CH_2CH_2C_8F_{17}$

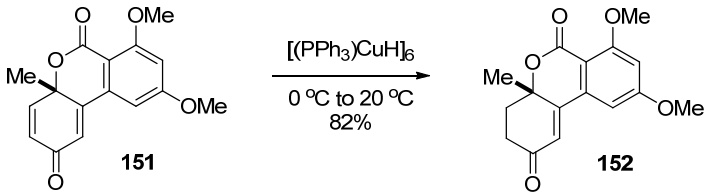
Scheme 42. Stryker's reagent in the synthesis of four stereoisomers of cytostatin.[85]

In 2008 Perez and Micalizio reported the synthesis of complex polyketides *via* titanium mediated C-C coupling.[87] They demonstrated the utility of this approach in the synthesis of spirocyclic polyketide **150**. Enone **149** was reduced with Stryker's reagent without protecting the free alcohol-groups (Scheme 43). Finally, the TES-protection was removed with camphorsulfonic acid, which also initiated the subsequent spirocyclization.



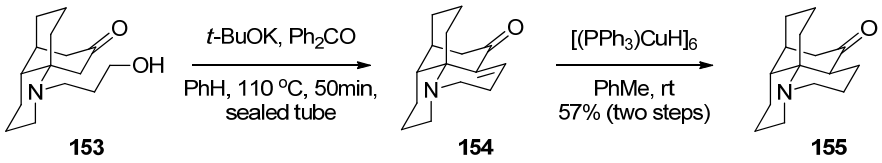
Scheme 43. Stryker's reagent in the synthesis of polyketides.[87]

Barrrett and co-workers synthesized dehydroaltenuene B *via* a delicate dienone **151** (Scheme 44).[88] Stryker's reagent selectively reduced the less substituted double bond and gave the enone **152** in good 82% yield.



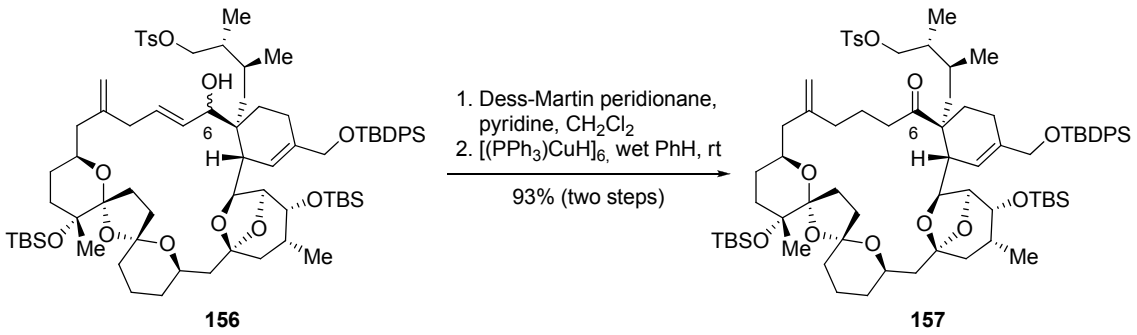
Scheme 44. Selective reduction of less substituted enone double bond.[88]

In 2008 Carter and co-workers reported the first enantioselective synthesis of lycopodine **155** (Scheme 45).[89] The last steps of their synthesis consisted of Oppenauer oxidation of keto-alcohol **153**, which underwent an intramolecular aldol condensation into the tetracyclic enone **154**. The enone was reduced with Stryker's reagent to give lycopodine **155** in 57% yield over two steps.



Scheme 45. Last steps of the total synthesis of lycopodine **155**.[89]

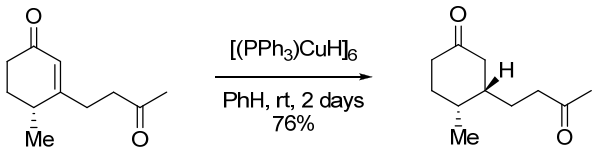
Hashimoto and co-workers demonstrated the utility of Stryker's reagent in the late stages of a total synthesis of pinnatoxin A.[90] Allylic alcohol **156** was oxidized at C6 to the corresponding enone (Scheme 46). This enone was selectively reduced to the ketone **157** in a staggering 93% yield, without affecting the multiple spirocyclic acetals, isolated double bonds or primary tosylate.



156 **157**

Scheme 46. Stryker's reagent in the synthesis of pinnatoxin A.[90]

Altmann and co-workers used Stryker's reagent in the first total synthesis of valerinic acid in 2009.[91] They reduced enone **158** to the corresponding ketone **159** in good yield and single stereoisomer (Scheme 47). Interestingly, the compound did not undergo reductive aldol reaction in these conditions, although it was planned to be the next step in their synthesis.

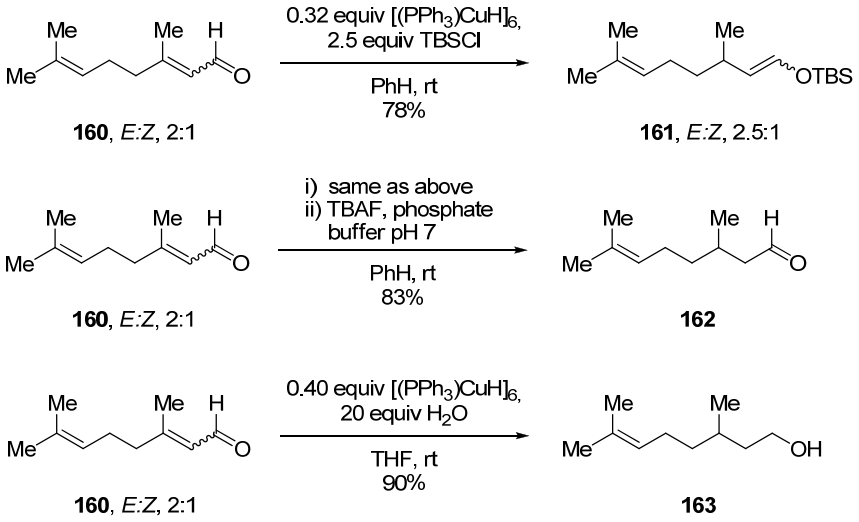


158 **159**

Scheme 47. Conjugate reduction in the total synthesis of valerinic acid.[91]

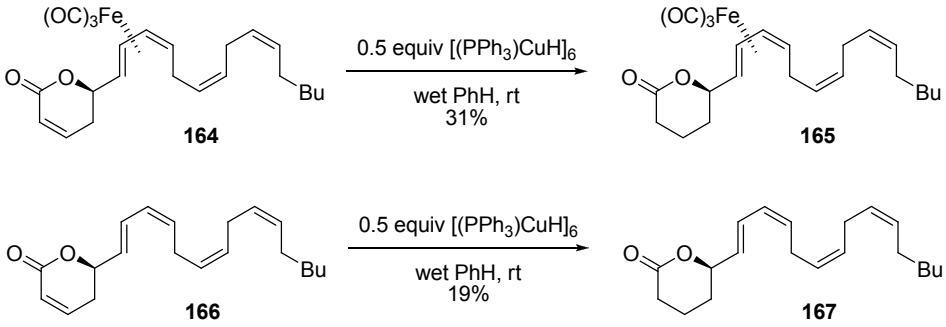
3.1.2 Stryker's reagent in the reduction of other α,β-unsaturated systems

Stryker and co-workers already showed in their original paper in 1988 that $[(PPh_3)CuH]_6$ is capable of reducing α,β-unsaturated ketones and esters.[44] In a following paper in 1989 they expanded the scope of their new reagent to include the reduction of α,β-unsaturated aldehydes.[92] When the reduction of a 2:1-mixture of citral and neral was done in the presence of *tert*-butyl dimethylsilyl chloride, a similar mixture of the corresponding silyl enolates **161** was obtained (Scheme 48). Quenching the reaction with TBAF gave the α,β-saturated aldehyde **162**. When the reduction was conducted in wet conditions, the 1,4-reduction is followed by a 1,2-reduction, and the fully saturated alcohol **163** is obtained.



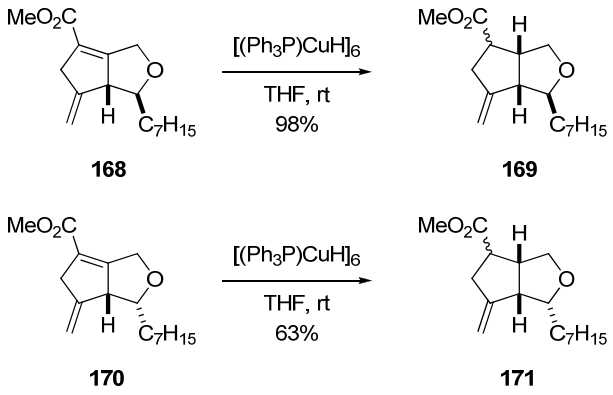
Scheme 48. Stryker conjugate reduction involving aldehydes.[92]

Tao and Donaldson published in 1993 an early example of target-oriented use of Stryker's reagent in the synthesis of 5-hydroxyeicosatetraenoic acid and its metabolite derivatives.[93] They reduced the α,β-unsaturated lactone **164**, which contained an iron η^4-diene complex to the saturated lactone **165** in only 31% yield (Scheme 49). Oxidative removal of the iron complex prior to reduction made the situation even worse, and the yield dropped to 19%. The carboxylate is in an allylic position relative to the diene, which can cause decomposition or unwanted allylic reductions.



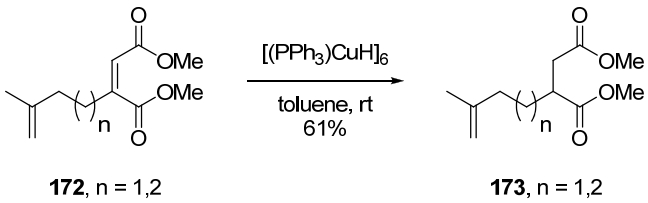
Scheme 49. Stryker's reagent in the synthesis of 5-hydroxyeicosatetraenoic lactone **2**.[93]

In 1996 Lautens *et al.* demonstrated the utility of reaction products from [3+2] –cycloadditions by using Stryker's reagent in the derivatization process (Scheme 50).[94] Conjugated esters **168** and **170** were reduced to their corresponding saturated ester partners **169** and **171**. New β-stereocenters were formed with full control, but α-stereocenters gave only 1.6:1 - 1.7:1 ratios.



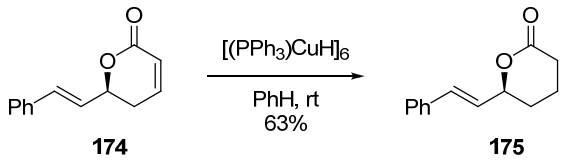
Scheme 50. Copper reductions by Lautens *et al*.[94]

Vederas and co-workers have synthesized some isopentenyl diphosphate analogues.[95] They used Stryker's reagent to reduce modified maleates **172** to their saturated diesters **173** retaining the isolated double bonds (Scheme 51).



Scheme 51. Stryker's reagent in the synthesis of isopentenyl diphospate analogues.[95]

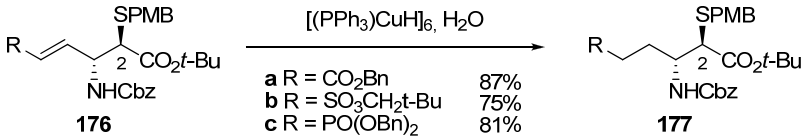
Pilli and co-workers have investigated the cytotoxic properties of (*S*)-goniothalamin **175** (Scheme 52).[96] They were interested in the role of α,β-unsaturation of the lactone in biological activity. By removing this functionality with Stryker's reagent, they were able to distinguish this functionality to be essential for the pharmacophore.



Scheme 52. Conjugate reduction in the synthesis of (*S*)-goniothalamin **175** analogue.[96]

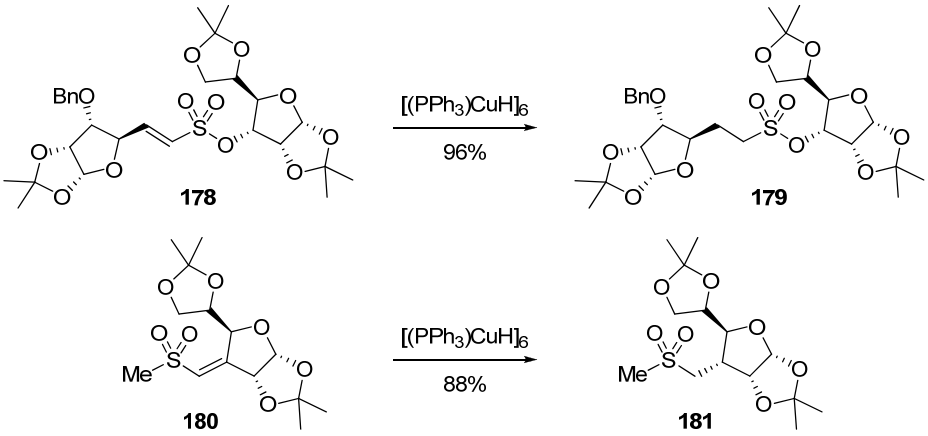
In 1999 Roques and co-workers reported the synthesis of potent aminopeptidase inhibitors.[97] Their synthesis strategy contained the reductions of α,β-unsaturated ester **176a**, sulfonate **176b**, and phosphonate **176c** (Scheme 53). Initially they used sodium borohydride in the saturation process, but observed complete racemization at the C2

stereocenter. Other functionalities such as Cbz, PMB and Bn prevented the use of catalytic hydrogenation. The solution to this problem was to use Stryker's reagent in the conjugate reduction, which resulted in good yields in all cases. Diastereomeric purity at C2 of **177b** was observed to drop to 4:1, favouring the desired one. They were satisfied with this result and conducted the reactions in multigram scale (1.4-12 g).



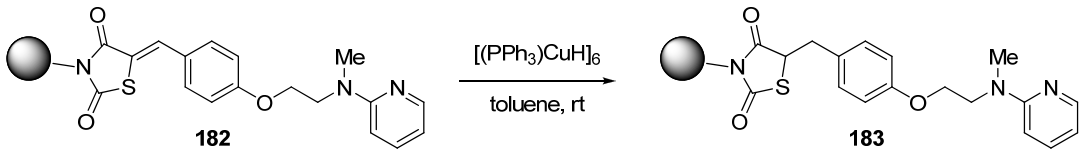
Scheme 53. Stryker's reagent in the gram scale synthesis aminopeptidase inhibitors.[97]

In 1991 Musicki and Widlanski reported a synthesis of nucleoside sulfonates and sulfones.[98] They built the α,β-unsaturated sulfonate **178**, which was first reduced with sodium borohydride in good 85% yield (Scheme 54). Stryker had reported in 1990 that sulfonates are tolerated by their new reagent.[59] Commercially available Stryker's reagent gave a much higher yield of 96% for the conjugate reduction of **178**. Similarly, sulfone **180** was selectively reduced to **181** in good 88% yield.



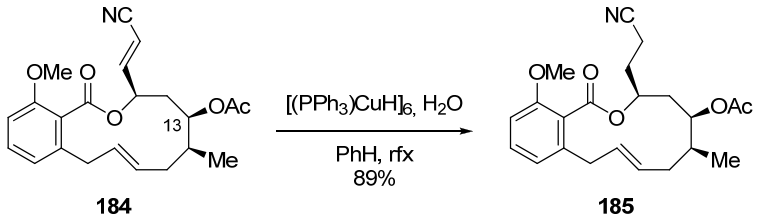
Scheme 54. Reduction of α,β-unsaturated sulfonate and sulfone in carbohydrate chemistry.[98]

Brummond and Lu synthesized BRL 49653 on solid support in 1999 (Scheme 55).[99] They used the selective reduction methodology suitable for solid phase synthesis developed earlier by Bolton *et al.* (Scheme 22).[65] Conjugated amide **182** was reduced with Stryker's reagent to give the corresponding saturated amide **183**. BRL 49653 could be obtained by cleaving off the resin with standard conditions.



Scheme 55. Stryker's reagent in the solid phase synthesis of BRL 49653.[99]

Georg and co-workers used Stryker's reagent to saturate α,β-unsaturated nitriles in the total synthesis of (-)-salicylihalamides.[100] Initially, the C13-hydroxyl contained a *p*-nitrobenzoate functionality, which resulted in lower yields in the reduction (Scheme 56). Acetate was found to be a suitable protection and the reduction gave a good yield of the saturated nitrile **185**.



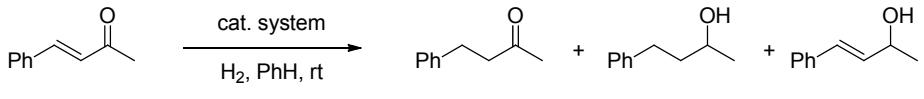
Scheme 56. Conjugate reduction of α,β-unsaturated nitrile in the formal total synthesis of (-)-salicylihalamides.[100]

Stryker's reagent has been widely used in the last 20 years in syntheses of complex targets. This relatively new hydride donor has proven to be highly selective in different conjugate reductions and can tolerate a variety of functional groups. It can be used to generate new stereocenters with high diastereoselectivity. One might argue that Stryker's copper hydrides and their applications are truly significant inventions, and they have found their place in the "toolboxes" of organic chemists.

3.2 Conjugate reduction with catalytic Stryker's reagent and hydrogen

In 1938 Calvin showed that some copper(II) salts can be used as a homogeneous catalyst for the hydrogenation of quinone and chloranil with molecular hydrogen in quinoline or chlororonaphtalene.[101] They reported that copper(II) acetate is reduced by hydrogen in an autocatalytic process to copper(I) species. This intermediate is probably stabilized by the coordinated quinoline and thus forms the actual hydrogenation catalyst. This was probably the first report of the use of copper hydride in substrate reduction, although the actual catalytic species was not identified. In a further study in 1956, Calvin and Wilmarth speculated that the formula of the active catalyst was $Cu^{I}H$ or the dimer $Cu^{I}_{2}H_{2}$.[102] Goeden and Caulton used the soluble tetrameric $(CuO\textit{t}\text{-}Bu)_4$ in the *hydrogenolysis* of formaldehyde in 1981.[103] This complex was shown activate molecular hydrogen in the presence of phosphine by forming stable *hydridic* hexamer $[CuHPR_3]_6$ and *tert*-butanol.

These early results were the basis for a later work by Stryker and co-workers in 1989, when they reported catalytic copper hydride reductions, which utilized molecular hydrogen as the stoichiometric reductant.[104] This work was an extension to their previous results on the use of $[(PPh_3)CuH]_6$ as a selective stoichiometric reductant for conjugate reductions of α,β-unsaturated ketones and esters.[44] Hydrogen is an atom economical and inexpensive reductant, which makes copper hydride-based catalytic reductions a very desirable methodology. They realized that Stryker's reagent is also a suitable catalyst for reducing various enones under hydrogen atmosphere. Unfortunately, selectivity towards 1,4-reductions was not uniform in all cases, and some 1,2-reduction products were also observed in different quantities (Scheme 57). Prolonged reaction times resulted in overreduction, which makes these reactions even more difficult to control. These methodologies also require rather high hydrogen pressures (500-1700 psi), which increases the explosion hazard. In a later study in 2000, Stryker and co-workers were able to increase the activity of their reductive system towards 1,2-reductions by changing the phosphine ligands.[105]

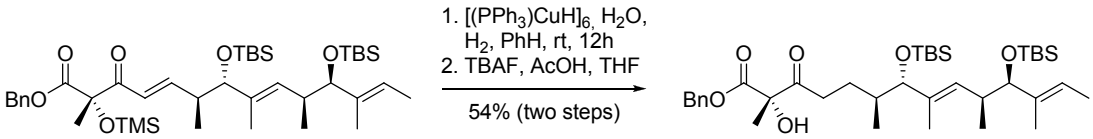


78 79 186 187

							Yield
(1) No added phosphine, 10h 2.7 mol% $[(Ph_3P)CuH]_6$, 1000 psi H_2	91	:	9	:	0		89%
(2) PPh_3 (12 equiv/Cu), 24h 2.7 mol% $[(Ph_3P)CuH]_6$, 1700 psi H_2	0	:	92	:	8		95%
(3) Me_2PPh (6 equiv/Cu), 10h 0.83 mol% $[(Ph_3P)CuH]_6$, 500 psi H_2	0	:	8	:	92		92%

Scheme 57. Stryker's conjugate reduction with hydrogen as reductant.[104,105]

Stryker's catalytic conjugate reductions with hydrogen have not gained widespread use. The only example using this technology found in the literature was reported by Hamada and co-workers in 2002.[106] They reduced enone **188** to the saturated ketone **189** using Stryker's reagent under hydrogen atmosphere (Scheme 58). It is unclear whether the reaction was truly catalytic, since the amount of Stryker's reagent was not reported.



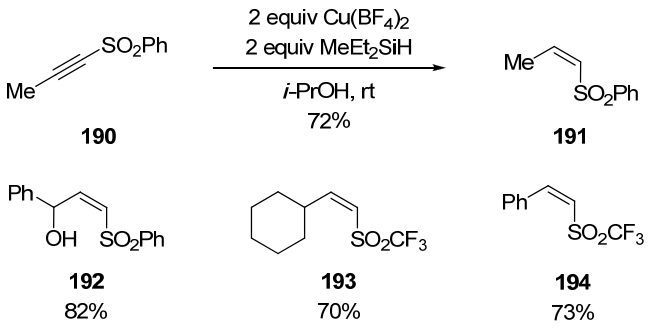
188 189

Scheme 58. Synthesis of side chain of hexadepsipeptide GE3.[106]

3.3 Conjugate reduction with catalytic copper hydrides and silanes

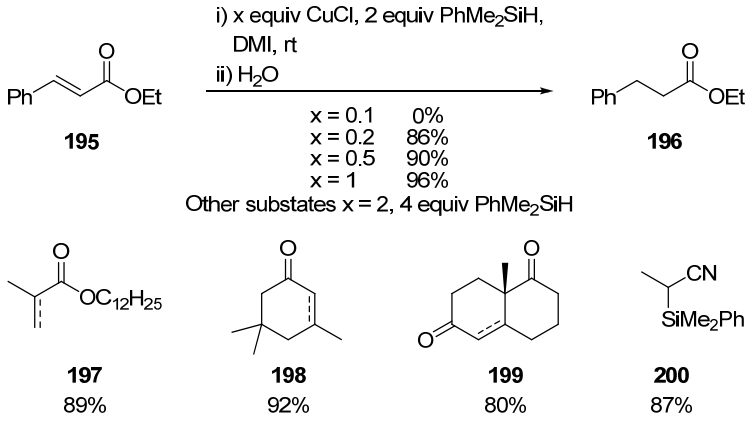
3.3.1 Stoichiometric copper hydride reductions

In 1989 Ryu *et al.* reported a generation of copper hydrides from copper(II) salts and Et_2MeSiH.[107] They assumed that this procedure results in copper(II) hydride, which was used to reduce acetylenic sulfones to *cis*-vinyl compounds (Scheme 59). The geometry of the newly formed double bond is possibly derived from *syn*-hydrocupration, since protonation of the sulfone enolate should give both geometrical isomers. These reaction conditions were not very successful in conjugate reductions of enones, and gave only moderate yields. Ryu's reagent was presumably a copper(I) hydride, since Lee and Yun later showed that copper(II) salts undergo reduction in the presence of silanes and form copper(I) hydride species.[46]



Scheme 59. First copper reductions using silanes as the stoichiometric reductant.[107]

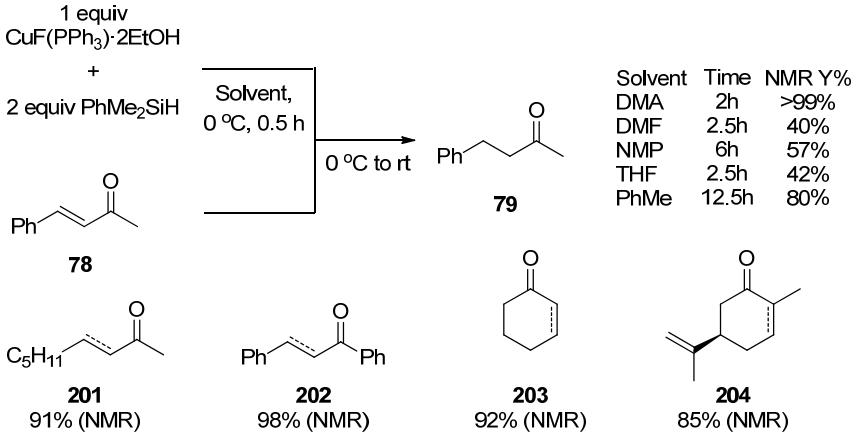
Nearly a decade later, in 1997 Hosomi and co-workers reported the generation of copper(I) hydride from $PhMe_2SiH$ and CuCl in highly polar solvents such as DMF and DMI.[108] Other silanes such as Et_3SiH and Ph_2SiH_2 also showed activity in the σ-bond metathesis. They were able to show that copper can act as catalyst, when α,β-unsaturated ester **195** was reduced with various amounts of copper(I) chloride in the presence of 2 equivalents of $PhMe_2SiH$ (Scheme 60). Unfortunately, the yields dropped when less than stoichiometric amounts of copper was used, and they chose to use excess of CuCl and silane in further experiments. Their reductive system was suitable for the reduction of α,β-unsaturated esters, ketones and nitriles.



Scheme 60. An early example of general conjugate reduction with copper and silanes.[108]

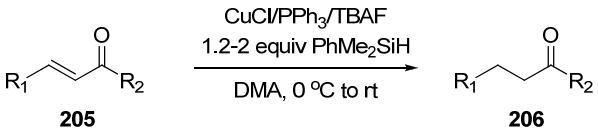
An alternative procedure was reported by Mori *et al.* also in 1997.[109] They tested various copper sources and found that the stable copper(I) fluoride complex, $CuF(PPh_3)_2$•2EtOH was most suitable for the generation of copper hydride from silanes such as $PhMe_2SiH$, Et_3SiH, $(EtO)_3SiH$ and Ph_2SiH_2. Solvent screen showed that DMA

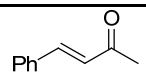
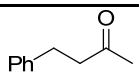
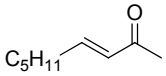
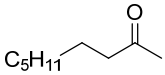
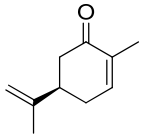
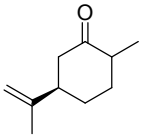
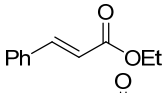
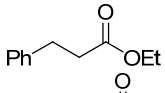
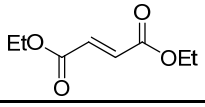
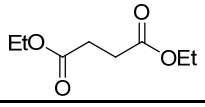
was the most potent solvent, although toluene also gave relatively good results (Scheme 61). This stoichiometric reaction was capable of reducing various enones to the corresponding ketones. This system also proved to be catalytic, when 5 mol % of $CuF(PPh_3)_2$•2EtOH and 2 equivalents of $PhMe_2SiH$ were able to reduce enone **78** to the ketone **79** in 69% yield. Another alternative was to generate copper(I) fluoride *in situ* from CuCl, PPh_3 and TBAF (Table 4). This methodology was catalytic in some cases but required stoichiometric amounts of copper for more challenging substrates.



Scheme 61. Copper hydrides derived from silanes and copper fluoride complex.[109]

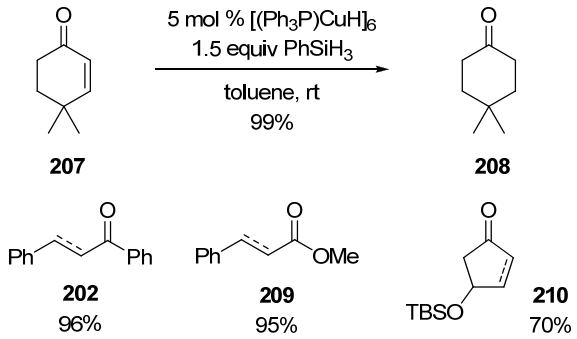
Table 4. Conjugate reduction using copper hydride derived from *in situ* CuF.[109]



Entry	Substrate	CuCl:PPh_3:TBAF (mol %)	Time (h)	Product	Yield (%)
1		20:20:10	2		88
2		25:25:20	2		77
3		160:160:150	4.5		87
4		20:20:10	4.5		54
5		110:110:100	2		65

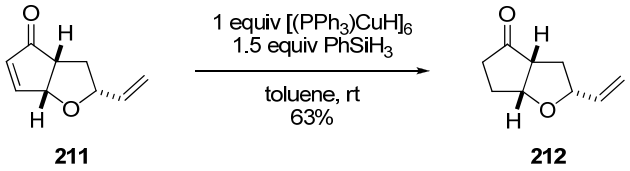
3.3.2 Catalytic copper hydride reductions

A major development in copper hydride methodology was made when Lipshutz *et al.* reported in 1998 that catalytic conjugate reductions could be performed with catalytic amounts (0.5-5 mol %) of isolated Stryker's reagent and Bu_3SnH or $PhSiH_3$ as the stoichiometric hydride source (Scheme 62).[47a] This methodology proved to be general and was suitable for selectively reducing α,β-unsaturated ketones, esters and aldehydes in high yields.



Scheme 62. Copper hydride catalyzed conjugate reductions with silanes.[47a]

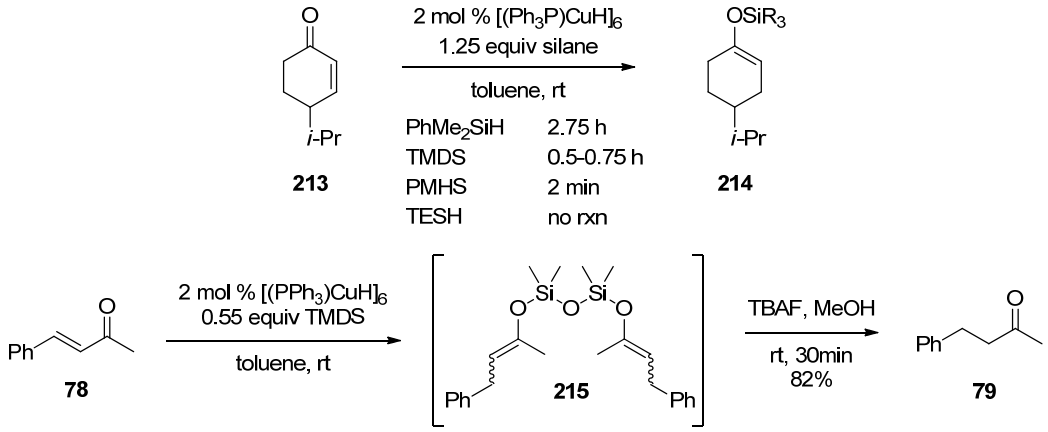
Chandler and Phillips utilized the Lipshutz methodology in the synthesis of (±)-*trans*-kumausyne.[110] They reduced enone **211** to the ketone **212** in a moderate 63% yield without reducing the terminal double bond (Scheme 63). Strangely, they chose to use a stoichiometric amount of Stryker's reagent, which could explain the reduced yield.



Scheme 63. Copper hydride reduction in the total synthesis of (±)-*trans*-kumausyne.[110]

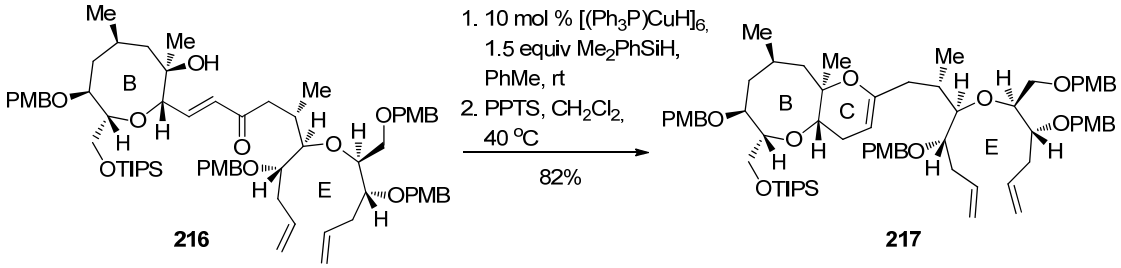
In 2000 Lipshutz *et al.* modified their previous method by changing $PhSiH_3$ to more economical alternatives such as dimethylphenylsilane, tetramethyldisiloxane (TMDS) and polymethylhydrosiloxane (PMHS) (Scheme 64).[47b] Conversion of the enone **213** with different silanes was monitored, and the reactivity followed the order of PHMS > TMDS > $PhMe_2SiH$ from the fastest reaction to the slowest. Triethylsilane was found to be inactive. With PMHS the amount of Stryker's reagent could be lowered to

0.2-1 mol % without losing activity, although the reaction rate decreased. In this publication Lipshutz and co-workers focused on reductive aldol reactions and gave only one example of a conjugate reduction of an enone to its saturated ketone. Reduction of enone **78** by using TMDS gave the dimeric silyl enolate **215**. Removal of silane with TBAF in methanol gave the ketone **79** in a good 82% yield.



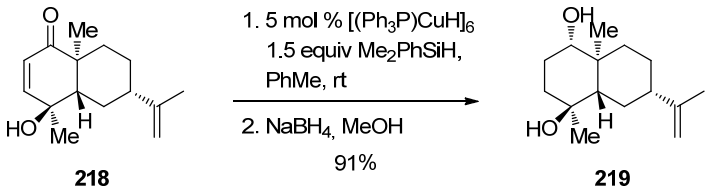
Scheme 64. Modified Lipshutz's protocol for copper hydride reductions.[47b]

Crimmins *et al.* showed the utility of this methodology in the synthesis of the BCDE fragment of brevetoxin A.[111] They reduced the enone **216** to the corresponding saturated ketone, which was directly transformed to endocyclic enol ether **217** in 82% total yield. Unprotected alcohol in the B-ring did not affect the reaction, and none of the protective groups were lost in the process.



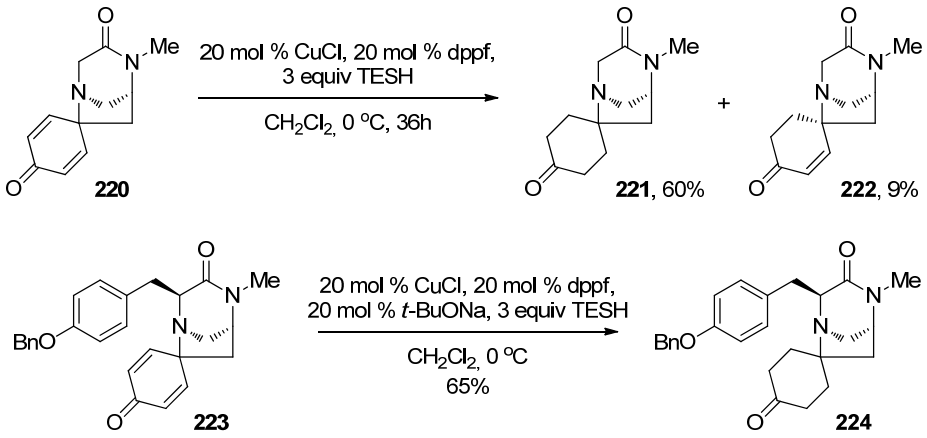
Scheme 65. Conjugate reduction in the synthesis of the BCDE fragment of brevetoxin A.[111]

In 2008 Pardeshi and Ward used Lipshutz's methodology in the final steps on the total synthesis of lairdinol A **219** (Scheme 66).[112] Enone **218** was reduced to the corresponding saturated ketone, which was further reduced with sodium borohydride to lairdinol A **219** in a high 91% total yield.



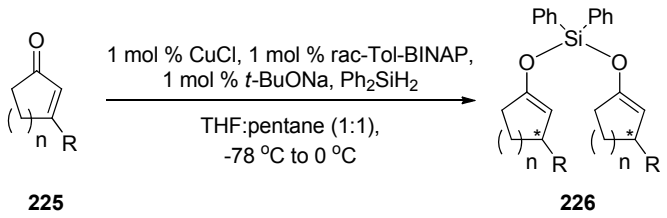
Scheme 66. Copper reduction in the total synthesis of lairdinol A **219**.[112]

In 2002 Honda and co-workers reported[113] a non-asymmetric method for conjugate reduction of enones, which was modified from Buchwald's enantioselective copper hydride reduction conditions (Scheme 67).[114] They changed the chiral ligand to achiral dppf, PMHS to Et_3SiH, and increased the catalyst loading from 5 mol % to 20 mol %. With these modifications they were able to reduce the enones **220** and **223** to the corresponding saturated ketones in moderate yields.



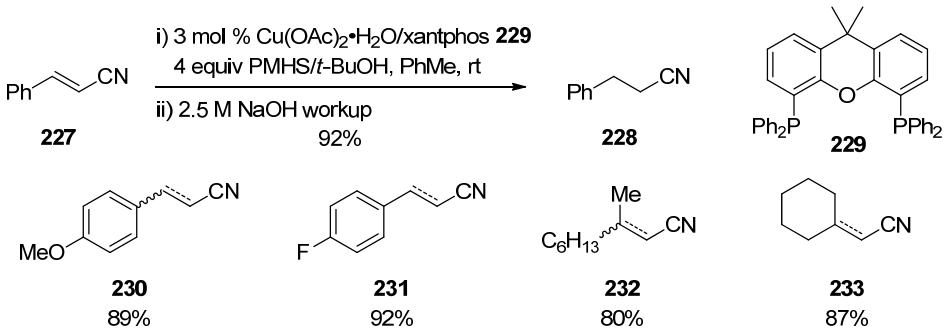
Scheme 67. Copper reductions in the synthesis of (−)-TAN1251A, TAN1251C TAN1251D.[113]

In 2004 Buchwald and co-workers published a study on enantioselective copper catalyzed conjugate reductions followed by α-arylation of the intermediate silyl enol ethers.[115] In order to analyze the enantiomeric excess, they synthesized the corresponding racemates by using the same procedure but changed the ligand to racemic Tol-BINAP (Scheme 68). This ligand is very expensive even as a racemate, which makes the utility of this methodology questionable.



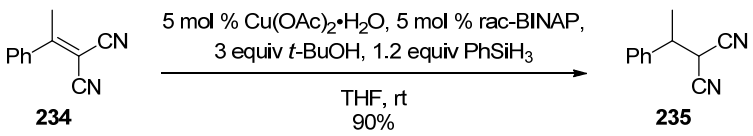
Scheme 68. Buchwald's synthesis of racemates.

In 2005 Yun and co-workers reported the reduction of α,β-unsaturated nitriles with copper hydride stabilized by xantphos ligand **229** (Scheme 69).[116] Instead of copper(I) salt, they used copper(II) acetate which undergoes a reduction to copper(I) hydride in the presence of silane, for example PMHS.[46] Other phosphines such as dppp and BINAP were less active, and dppb was totally inactive. DPEphos [2,2'-bis(diphenylphosphino)-diphenyl ether] was found to be equally active but gave a slightly lower yield of **228**. The use of *tert*-butanol was required to recycle the catalyst *via* copper *tert*-butoxide.



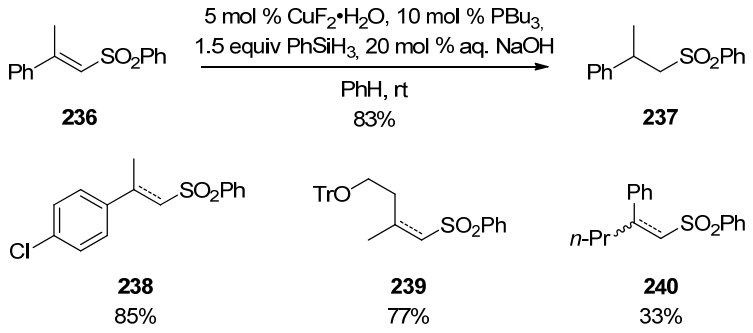
Scheme 69. Catalytic reduction of α,β-unsaturated nitriles.[116]

Xu and co-workers reported in 2005 a very similar catalytic system, whose main focus was on enantioselective conjugate reductions of α,β-unsaturated malononitriles (Scheme 70).[117] Their initial condition screening was done with racemic BINAP. Optimal conditions are almost identical to those reported in the concurrent study from Yun.[116] In Xu's system the silane was $PhSiH_3$ and solvent was THF. These catalyst systems also exhibit similar reactivity.



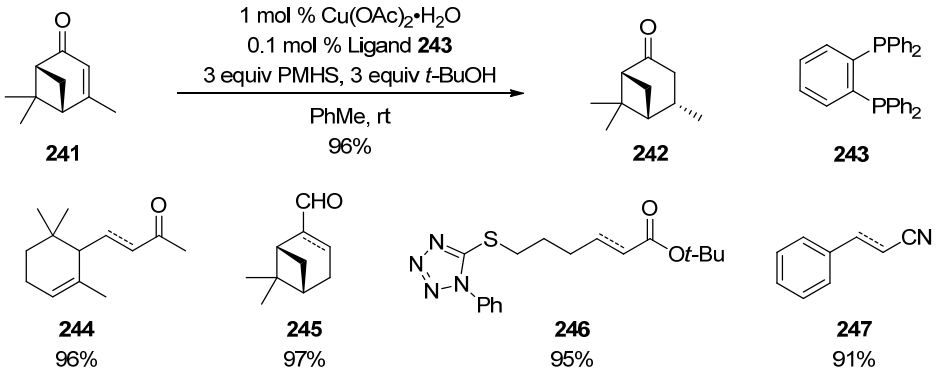
Scheme 70. Conjugate reduction of α,β-unsaturated malononitriles.[117]

Desrosiers and Charette published a copper hydride catalyzed reduction of α,β-unsaturated sulfones in 2007.[118] Their main focus was on enantioselective synthesis but they also reported a non-asymmetric method, which used tributylphosphine as the ligand and copper(II) fluoride as the copper source (Scheme 71). Phenyl silane gave higher yields than PMHS or $PhMeSiH_2$. They also observed that aqueous sodium hydroxide including two equivalents of water was necessary to increase the yield.



Scheme 71. Conjugate reduction of α,β-unsaturated sulfones.[118]

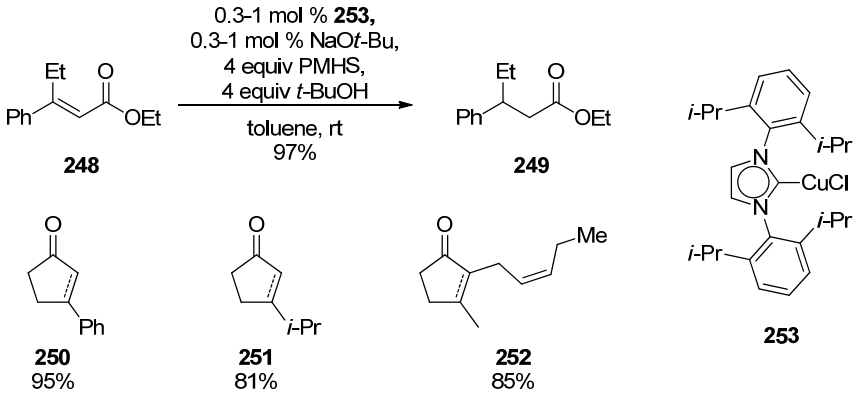
In 2008 Liphutz and co-workers reported a very active copper catalyst for conjugate reduction of various α,β-unsaturated functionalitites.[119] They used copper(II) acetate, bisphosphine ligand **243** (*o*-BDPPB or BDP) and PMHS to generate the copper hydride catalyst *in situ* (Scheme 72). Interestingly, they used only one tenth of the amount of the ligand compared to copper salt. This catalytic system could also be stored as a stock solution and did not lose activity over a period of one month.



Scheme 72. A highly active copper hydride catalyst.[119]

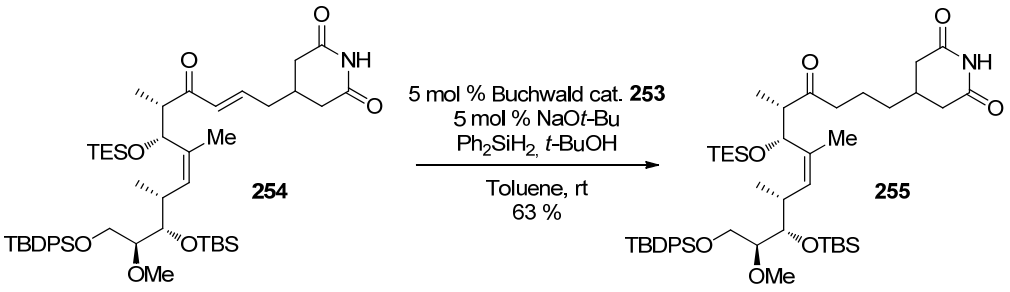
3.3.3 Conjugate reductions with NHC-stabilized copper hydride

In 2003 Buchwald and co-workers reported copper catalyzed conjugate reductions stabilized by a *N*-heterocyclic carbene (NHC) ligand.[120] These ligands have σ-bonding properties similar to bulky phosphines. Buchwald and co-workers generated their air and moisture stable catalyst complex **253** by deprotonation of 1,3-bis(2,6-di-*iso*propylphenyl)-imidazolium chloride with NaO*t*-Bu in the presence of copper(I) chloride (Scheme 73). The complex was activated with another equivalent of NaO*t*-Bu and PMHS as the stoichiometric hydride donor, which resulted in highly active copper hydride catalyst for conjugate reduction of various α,β-unsaturated esters and ketones.



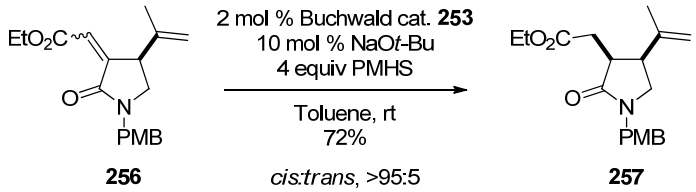
Scheme 73. First *N*-heterocyclic carbene (NHC) stabilized copper hydride.[120]

This methodology was used by Reymond and Cossy in the total synthesis of migrastatin.[121] They used Buchwald's catalyst **253** to reduce enone **254** to the saturated ketone **255** in moderate 63% yield (Scheme 74). The low yield led them to try catalytic hydrogenation with palladium on charcoal, which gave a much higher 96% yield, and therefore the copper hydride methodology was discarded.



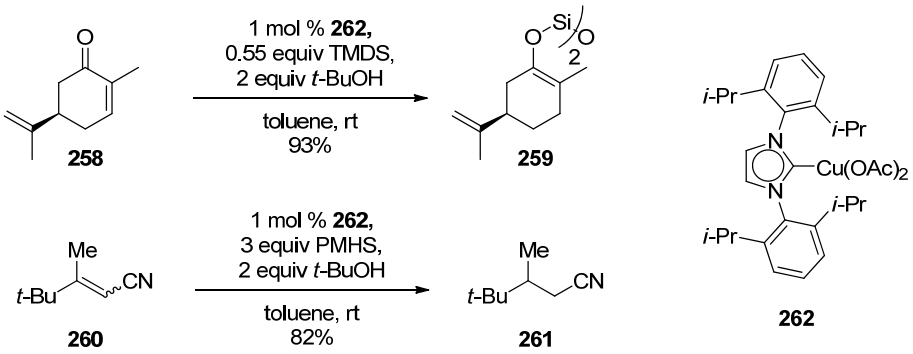
Scheme 74. NHC-stabilized copper hydride catalyzed reduction in the synthesis of migrastatin.[121]

In 2007 Poli and co-workers reported a total synthesis of (±)-kainic acid.[122] One of the stereochemistry-producing key steps was the conjugate reduction of ester **256** (Scheme 75). After failing with L-selectride they turned to copper hydride methodology. Buchwald's copper catalyst **253**, combined with NaO*t*-Bu and PMHS was able to reduce the α,β-unsaturated ester **256** to the saturated ester **257** in good yield and full diastereoselectivity.



Scheme 75. NHC-stabilized copper hydride catalyzed reduction in the synthesis of (±)- kainic acid.

In 2005 Yun and co-workers reported an alternative to Buchwald's catalyst.[123] They were able to complex copper(II) acetate with 1,3-bis(2,6-di-*iso*propylphenyl)-imidazolium ylidene and thus obtain the air and moisture stable catalyst **262** (Scheme 76). This complex could by characterized by x-ray crystallography. The major difference between Buchwald's catalyst **253** and Yun's catalyst **262** is that the latter does not require preactivation with NaO*t*-Bu, but undergoes direct formation of copper hydride in the presence of silanes. Their catalyst was tested in 1,2-reductions of aldehyde and ketone, and conjugate reductions of enones and nitriles.



Scheme 76. Conjugate reductions using air and moisture stable NHC precatalyst.[123]

Catalytic copper hydride reductions receive ever-growing interest, and several methods for reductions for various α,β-unsaturated systems have been reported. Most of the

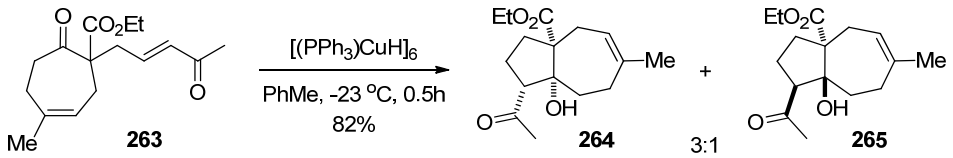
methods have not been used in target-oriented synthesis, which would provide further information on the utility of these catalyst systems. In recent years some promising, highly active *in situ* catalyst systems have been introduced, which may offer very good alternatives for the well established stoichiometric Stryker's reagent.

3.4 Reductive tandem reactions with copper hydrides

Substrates in tandem reactions are designed in such a way that the first transformation will generate a reactive intermediate, which will undergo a second or multiple transformations. In this section the focus is on reductive tandem reactions catalyzed by copper hydrides. Many of the presented reaction conditions are suitable for simple conjugate reductions, although the major focus of these studies has been on tandem reactions.

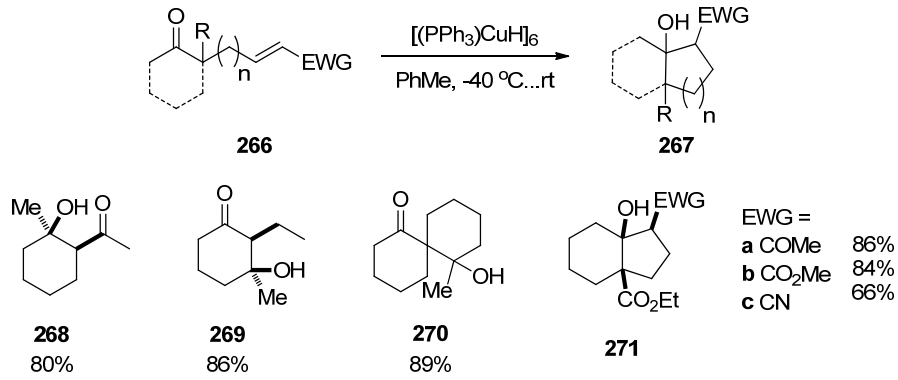
3.4.1 Reductive cyclization with stoichiometric Stryker's reagent

In 1998 Chiu *et al.* reported the first example of a reductive aldol reaction with Stryker's reagent in the synthesis towards pseudolaric acid A.[124] They noticed that Stryker's reagent was able to induce reductive cyclization of enone **263** at room temperature to give two different isomers **264** and **265** in a 6:1 ratio (Scheme 77). When the reaction was performed at a lower temperature and in a non-coordinative solvent such as toluene, they obtained these isomers in a ratio of 3:1 (**264**:**265**), increasing the selectivity towards **265**. Unfortunately, the desired isomer **265** was obtained as a minor product.



Scheme 77. Recuctive cyclization with Stryker's reagent in the synthesis towards pseudolaric acid A.[124]

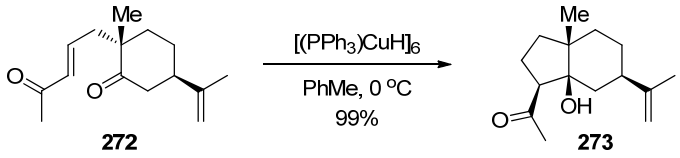
In a following paper in 2001, Chiu *et al.* reported further studies on their initial findings.[125] They extended the scope of reductive cyclizations on a variety of substrates with different substitution patterns (Scheme 78). The methodology was suitable to promote cyclization on five- and six-membered rings. A variety α,β-unsaturated ketones, esters and nitriles could be used to generate reactive enolates from double bonds, which were either *endo* or *exo* to the newly formed ring systems.



266 **267** **268** 80% **269** 86% **270** 89% **271**

Scheme 78. General reductive cyclizations with Stryker's reagent.[125]

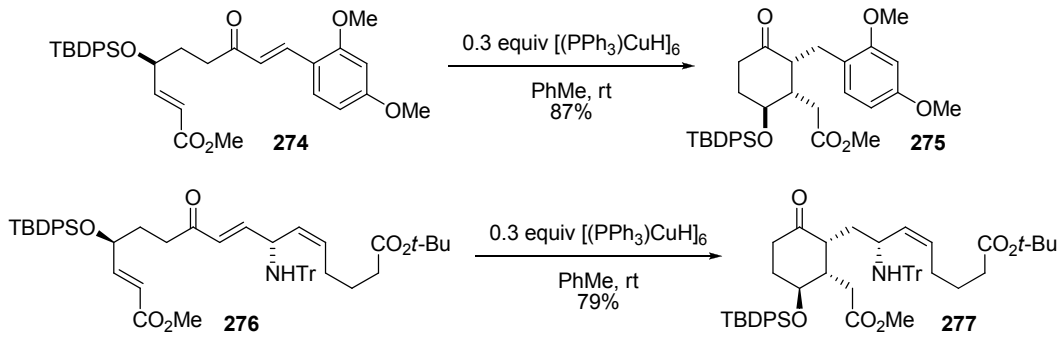
Chiu *et al.* demonstrated their methodology in action in the total synthesis of lucinone.[126] Enantiopure **272** was derived from carvone and underwent reductive intramolecular aldol reaction when treated with Stryker's reagent (Scheme 79). The product **273** was obtained as a single diastereomer and in excellent yield and could be converted to lucinone by dihydroxylation.



272 **273**

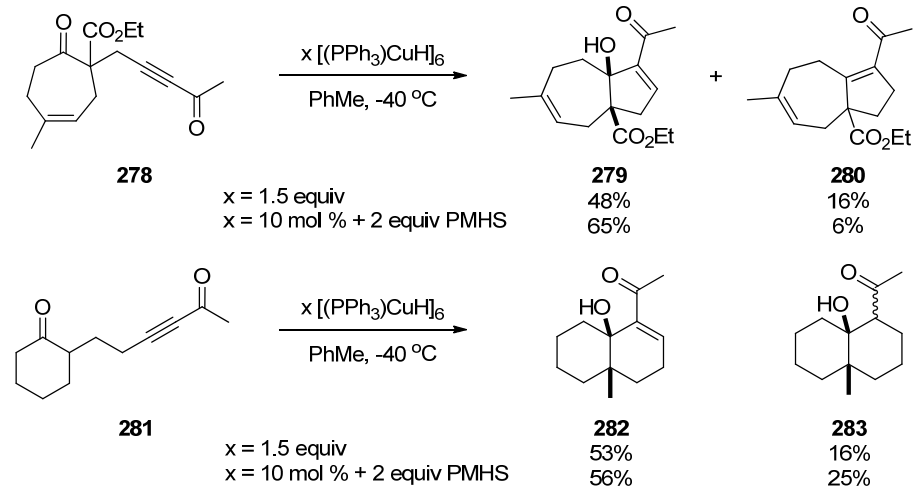
Scheme 79. Recuctive cyclization with Stryker's reagent in the synthesis of lucinone.[126]

In 2002 Overman and co-workers used Stryker's reagent to promote reductive intramolecular Michael reactions.[127] They showed existing stereocenters to induce high diastereoselectivity, and in most cases only one isomer was obtained (Scheme 80). α,β-Unsaturated esters and nitriles can be used as Michael acceptors when the enone acts as the initial electrophile for copper hydride.



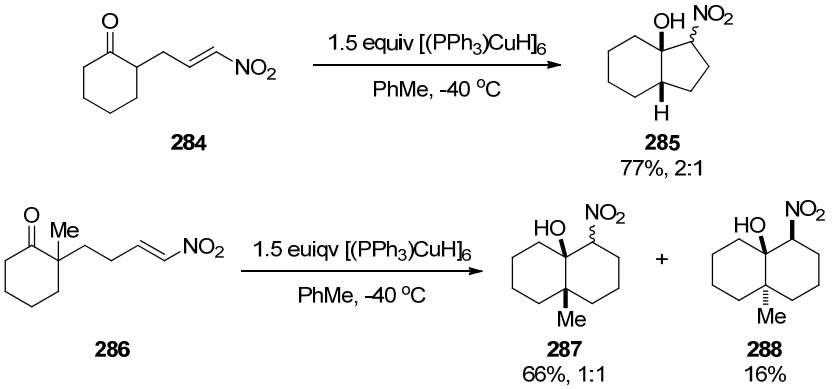
Scheme 80. Reductive Michael reactions with Stryker's reagent.[127]

In 2004 Chiu and Leung extended the scope of copper hydride catalyzed reductive cyclization on acetylenic compounds.[128] These reactions give products, which are generally obtained from Baylis-Hillman reactions. They used various substrates, which usually gave a mixture of products when treated with Stryker's reagent (Scheme 81). Stryker's reagent could also used as a catalyst when PHMS was used as the stoichiometric hydride donor.



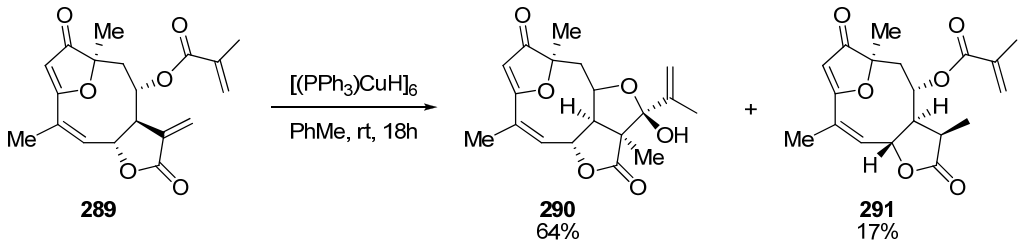
Scheme 81. Recuctive cyclization of acetylenic compounds.[128]

Another modification from Chung and Chiu was published in 2005 when they used Stryker's reagent on reductive intramolecular Henry reactions.[129] These reactions gave multiple diasteromers generally as 3:1-1:1 mixtures (Scheme 82). They also showed that Stryker's reagent is slightly basic, which might have caused some epimerization at α-stereocenters.



Scheme 82. Reductive Henry reactions with Stryker's reagent.[129]

Constantino and co-workers used Stryker's reagent to mimic a reductive pathway in the conversion of furanoheliangeolides to eremantholides proposed to occur in nature.[130] In shorter reaction times they obtained the non-cyclized derivative **291** as the major product (Scheme 83). When they extended the reaction time to 18 h, the intermediate copper enolate underwent conversion to eremantholide C **290** in a good 64% yield.

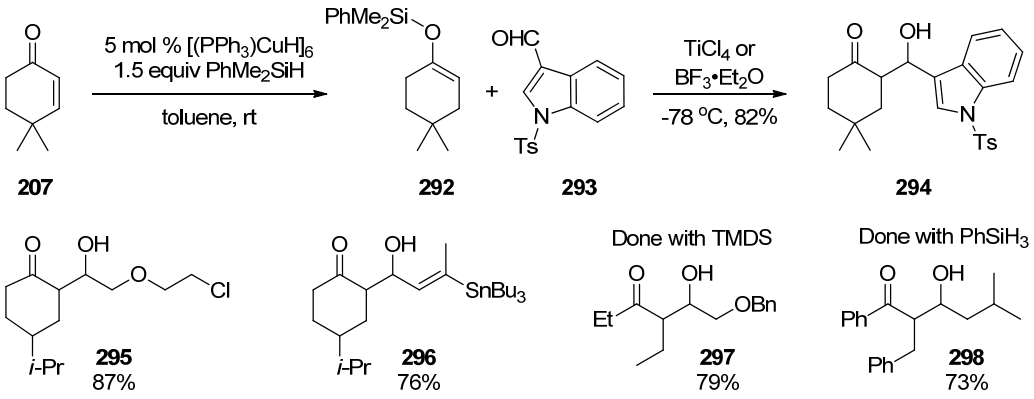


Scheme 83. Biomimetic conversion of a furanoheliangolide into an eremantholide C **290** with Stryker's reagent.[130]

3.4.2 Reductive tandem reactions with catalytic copper hydrides

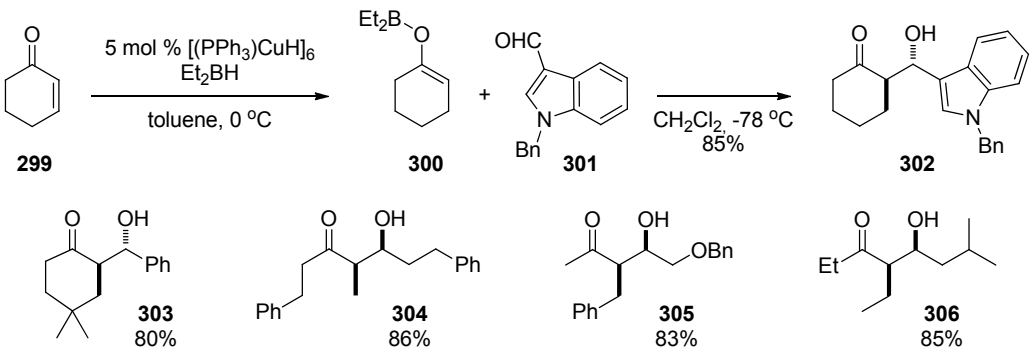
In 2000 Lipshutz *et al.* reported the first reductive aldol reactions performed with a catalytic amount of copper hydride (Scheme 84).[47b] This work was an extension on their previous work on 1,4-reductions with catalytic Stryker's reagent using $PhSiH_3$ as stoichiometric hydride donor.[47a] They substituted the silane with more economical alternatives such as $PhMe_2SiH$, TMDS and PMHS, and tested the scope by isolating some of the silyl enol ethers. After successful initial tests, they used this methodology in one pot reductive Mukaiyama aldol reactions by exposing the *in situ* generated silyl enol ethers to Lewis acids in the presence of aldehydes. Generally good overall yields

were obtained without affecting other functional groups. Aldehydes could not tolerate these reductive conditions and underwent 1,2-reductions if added prematurely. Stereochemical control was found to be poor, and a mixture of diastereomers was obtained.



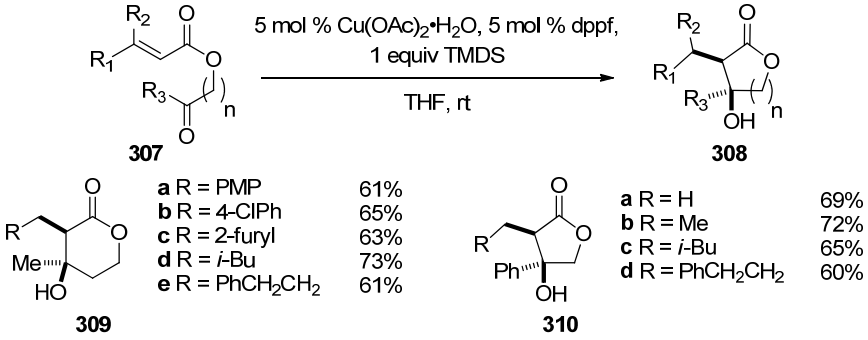
Scheme 84. Reductive Mukaiyama aldol reactions with copper hydrides.[47b]

Lipshutz and Papa further developed these reductive aldol reactions by changing the stoichiometric hydride donor to diethylborane (Scheme 85).[131] This modification gave excellent control on the geometry of intermediate boron enolates. Acyclic enones gave thermodynamically favoured *Z*-enolates, which underwent aldol reactions with aldehydes and produced *syn*-aldol products in good yields and single diastereomers. Cyclic enones, giving *E*-enolates in the process, afforded *anti*-aldol products. Disadvantages of these methodologies are the *in situ* the production of Et_2BH from equilibration of Et_3B with BH_3•THF, and the need to change the solvent to dichloromethane between reaction steps. They also showed that diisopinocamphenylborane and pinacolborane are good alternatives for hydride donors.



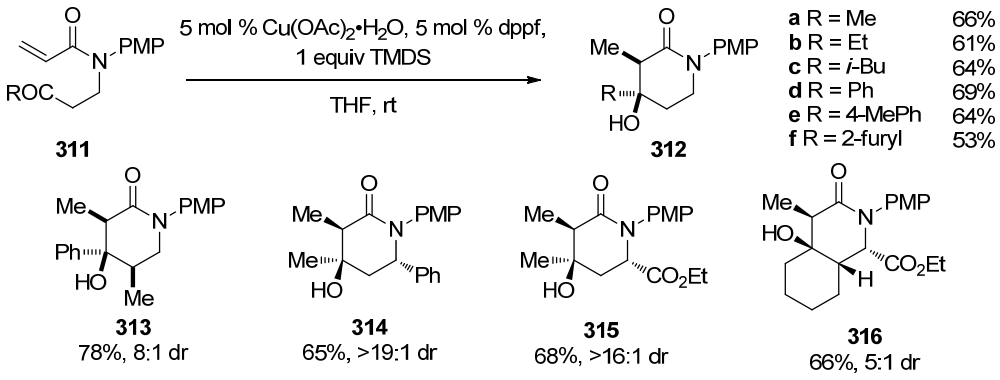
Scheme 85. Reductive aldol reactions with borohydrides and copper.[131]

In 2005 Lam and Joensuu described reductive cyclizations using an *in situ* generated copper hydride catalyst.[132] Among the various copper sources tested, $Cu(OAc)_2•H_2O$ and Cu(2-ethylhexanoate)$_2$ proved to be the most suitable ones (Scheme 86). A variety of ligands was also tested, which showed that rac-BINAP and dppf were suitable to create the active catalytic species. Ligands such as dppe, dppb and (*S,S*)-Et-DuPhos were found to be almost inactive. Inexpensive PMHS and TMDS silanes were found to give higher yields than Et_3SiH, $Me(EtO)_2SiH$ or $(EtO)_3SiH$. The optimized conditions were used in reductive aldol reactions of various α,β-unsaturated esters **307** to form five- and six-membered β-hydroxy lactones **308**. Diastereoselectivity was found to be excellent and generally the products were obtained as single diastereomers.



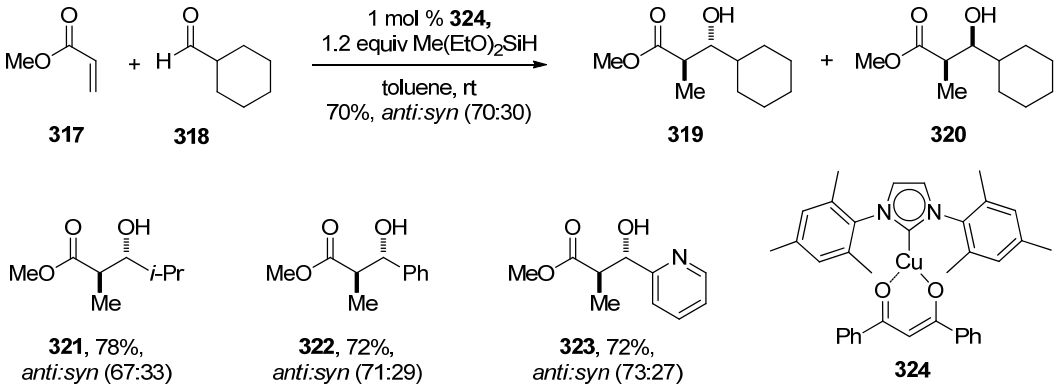
Scheme 86. Reductive cyclizations with copper hydride catalysis.[132]

In a following paper Lam *et al.* extended the use of this methodology on the synthesis of β-hydroxy lactams (Scheme 87).[133] Similarly, products were obtained in excellent diastereoselectivity usually as single isomers. They also tested internal chiral induction by introducing stereocenters at strategic positions. These examples showed that the new stereocenters could be generated in good diastereoselectivities.



Scheme 87. Reductive cyclizations with internal asymmetric induction.[133]

In 2006 Riant and co-workers performed some intermolecular reductive aldol reactions catalyzed by the NHC-copper complex **324** (Scheme 88).[134] They performed their initial experiments with $PhSiH_3$, and then began to look for more economical silane sources. TMDS, HMTS and $Me_2(EtO)SiH$ were found to be almost inactive. Good reactivities were obtained with Ph_2SiH_2 and slightly less expensive $Me(EtO)_2SiH$. Various aldehydes were reacted with methyl acrylate and methyl crotylate under optimized reductive conditions. Yields from these reductive aldol reactions were generally good, but diastereoselectivities were found to be poor in all cases.



Scheme 88. Reductive aldol reaction with copper-NHC catalyst.[134]

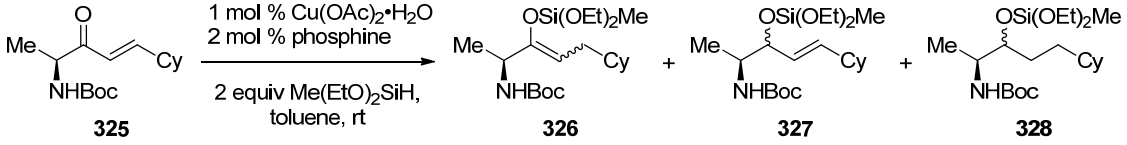
3.5 Conclusions

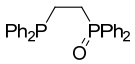
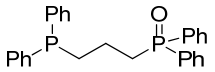
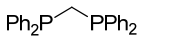
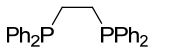
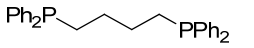
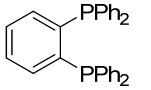
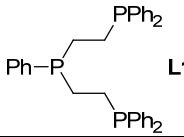
Copper hydrides have left their mark on the methodology of organic synthesis. Stryker's reagent is a widely used tool and has established its position as a mild chemoselective reductant. It is also a useful catalyst when combined with other stoichiometric hydride sources. The instability of Stryker's reagent towards oxygen detracts from its utility, since prolonged storage can cause major decomposition, and occasionally commercial material has very little activity left.[47b] This fact has led to the development of a new technology where copper hydride is formed *in situ* from suitable copper salts and hydride sources. Although recent literature focuses on enantioselective reactions,[135] there is still a demand for non-asymmetric copper hydrides and especially for a practical and economical catalytic copper hydride methodology.

3.6 Results and discussion

Early results on copper hydrides from amaminol A **1** synthesis led us to survey these reactions further.[136] Our aim was to develop a catalytic and highly selective method for the conjugate reduction of enones in the presence of slightly acidic NH-protons. Since ligands play a major role in the catalytic activity of copper hydrides, we chose to screen various monodentate and bidentate phosphorous ligands in a reduction of a model enone **325** (Table 5) in the presence of reliable $Cu(OAc)_2 \bullet H_2O$ and $Me(EtO)_2SiH$ (Table 2).

Table 5. Conjugate reduction model study.[136]

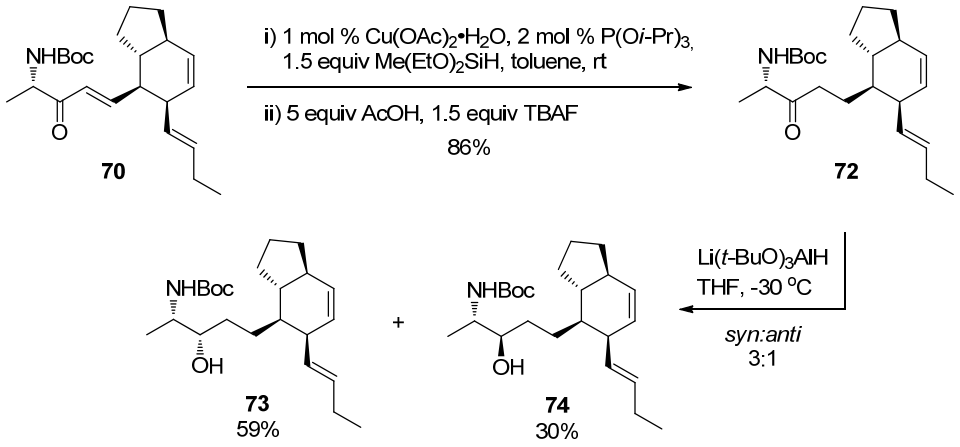


Entry	Ligand	Premix time[a]	Time	Ratio of **326:327:328**	Yield (%)[b] ketone:alcohol
1	PPh_3 **L1**	1 h	1.5 h	94:6:0	79:8
2	 **L2**	1.5 h	4 h	96:4:0	65:5
3	 **L3**	2 h	50 min	91:8:1	83:7
4	$P(Oi\text{-}Pr)_3$ **L4**	4 h	55 min	96:4:0	95:3
5	$P(OEt)_3$ **L5**	4 h	2h	96:4:0	77:4
6	 **L6**	1.5 h	9 h	92:6:2	82:9
7	 **L7**	1 h	15 min	48:50:2	43:49
8	 **L8**	2 h	3.5 h	54:46:0	43:36
9	 **L9**	1 h	35 min	49:49:2	42:43
10	 **L10**	1 h	18 h	10:81:9	9:71

[a] Time needed for catalytically active species to be formed (copper salt fully dissolved and occurrence of colour change). [b] Isolated yields after 1.5 equiv TBAF / 5 equiv AcOH quench and silica gel chromatography for ketone (from **326**) and alcohols (from **327** and **328**).

Monodantate ligands PPh_3, $P(Oi\text{-}Pr)_3$ and $P(OEt)_3$ showed comparable reaction times and selectivitites. Initial copper hydride formation of PPh_3 was faster than those of phosphites, but $P(Oi\text{-}Pr)_3$ gave the highest isolated yield of the ketone derived from **326** by TBAF quench. Phosphorous monoxides **L2** and **L3** showed similar behaviour as monodentate ligands. Bidentate ligands formed copper hydrides generally faster than monodentate ligands, but were less selective toward 1,4-reductions (entries 6-9). The fastest reactions were obtained with dppe **L7** and *o*-BDPPB **L9**, which showed significant activities but poor selectivities. Tridentate ligand **L10** was a poor candidate for copper hydride reductions. Based on these results, we chose to use $P(Oi\text{-}Pr)_3$ in the reduction of various substrates in order to screen the applicability of this method.[136]

We also used our new improved method in the synthesis of amaminol A **1**. Nearly a gram (0.83 g, 2.2 mmol) of enone **70** was reduced to the saturated ketone **72** in a good 86% yield, with some 5% of 1,2-reduction products also present (Scheme 89). This single experiment showed only minor improvement on the yield when compared to our old methodology with PPh_3, when 1.52 mmol of enone **70** was reduced to **72** in 84% yield (Table 2). However, purification became easier since PPh_3 has a similar retention time on silica gel chromatography as the product **72**, and $P(Oi\text{-}Pr)_3$ barely moves on silica gel. This ketone **72** was then reduced to the aminoalcohols **73** and **74** with $Li(t\text{-}BuO)_3AlH$ using conditions described previously (Table 3). Pure *N*-Boc-protected amaminol A **73** was isolated after silica gel chromatography in 59% yield together with a mixture of isomers in 30% yield.



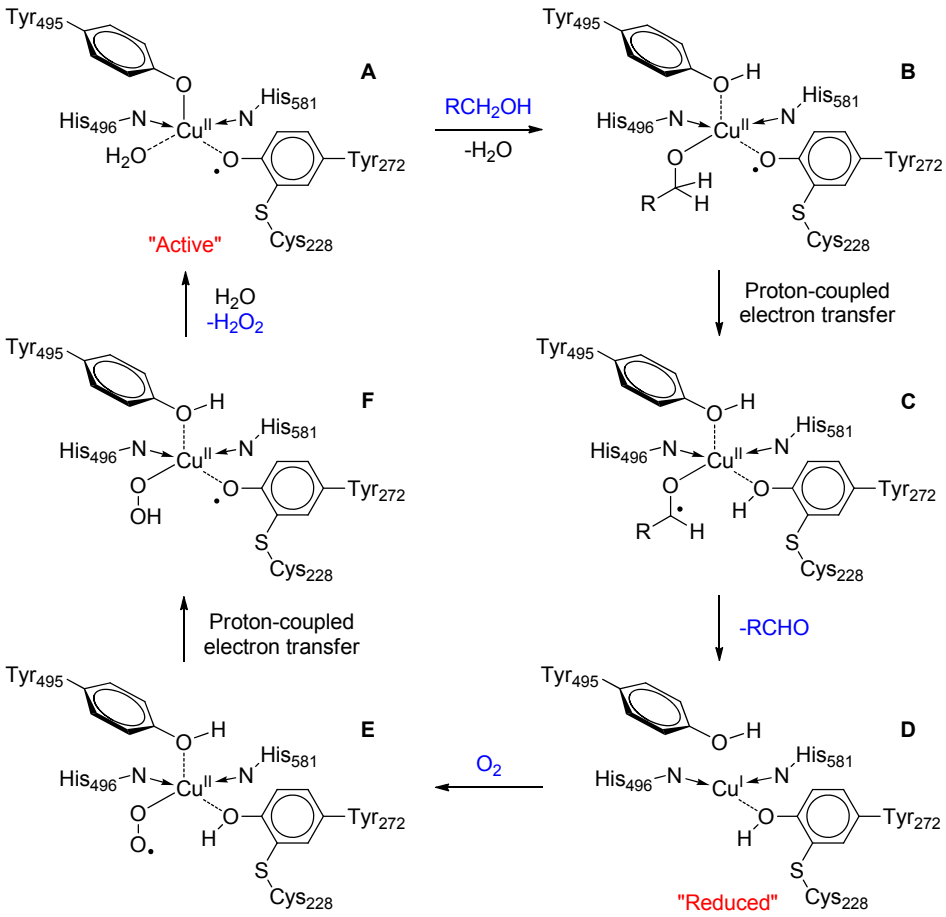
Scheme 89. Selective conjugate reduction in the synthesis of amaminol A **1**.

4 COPPER CATALYZED AEROBIC OXIDATIONS

Oxidation of alcohols to carbonyl compounds is one of the fundamental reactions both in nature and in organic synthesis. Synthetic chemistry heavily relies of stoichiometric oxidants[137] when nature uses metal catalysis and oxygen as the terminal oxidant.[138] The quest for replacing stoichiometric oxidants with a methodogy similar to nature has recently gained increasing interest.[139-141]

4.1 Bio-inspired alcohol oxidations

Galactose oxidase (GO) is a type II mononuclear copper enzyme which converts a variety of primary alcohols to aldehydes.[142] The active site incorporates a tyrosine residue as a radical mediator, which in combination with copper(II) can perform a two-electron oxidation process (Scheme 90). A generally accepted mechanism was reported by Whittaker and Whittaker.[143] The inactive form of GO undergoes an unknown one-electron oxidation process and forms the "active" catalyst **A**. Coordination of the substrate alcohol is followed by a single-electron oxidation process, where a tyrosine radical abstracts the α-proton from the alcohol. Another one-electron oxidation process reduces the copper(II) complex **C** to copper(I) complex **D** and gives an aldehyde as the product. Reduced copper(I) is reoxidized with molecular oxygen forming copper(II) superoxide **E**, which regenerates the tyrosine radical cofactor by a proton-coupled electron transfer. The resulting copper(II) hydroperoxide **F** undergoes a ligand exchange with water or another alcohol substrate and releases hydrogen peroxide in the process. Understanding this mechanism has played a major role in the development of galactose oxidase mimetics and other oxidation catalysts relying on radical cofactors.



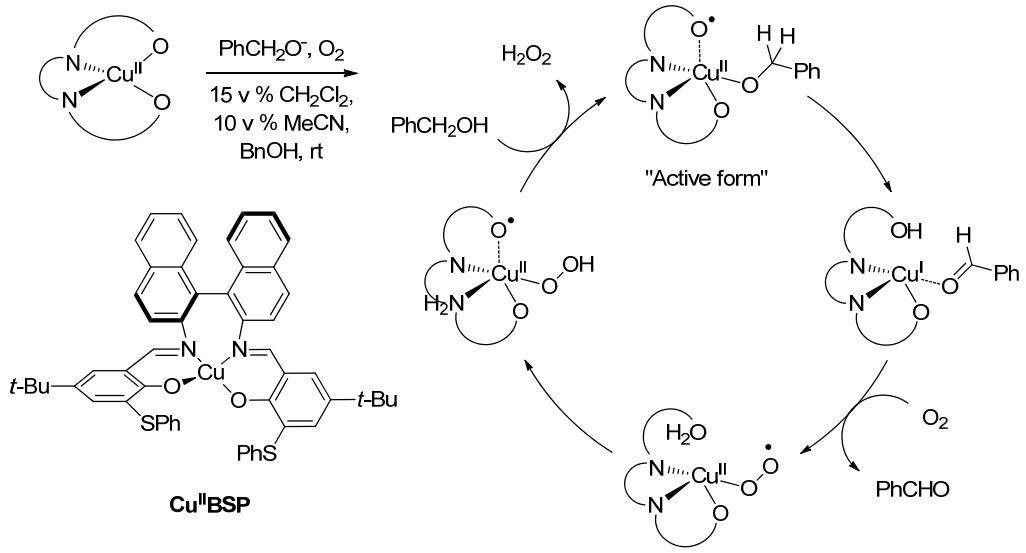
Scheme 90. Proposed mechanism of Galactose oxidase.[138b]

4.1.1 Galactose oxidase mimetics

Due to the efficiency of GO,[144] extensive research has been devoted to mimic its active site in order to produce a simple catalytic system for synthetic use. The scientific community has produced a variety of catalytically active GO mimetics over the past 10 years, and many review articles on these systems have been published.[145] Here I describe only a few important and highly active catalytic systems mimicking the active site of GO in order to compare these systems to other copper catalysts for oxidation of alcohols.

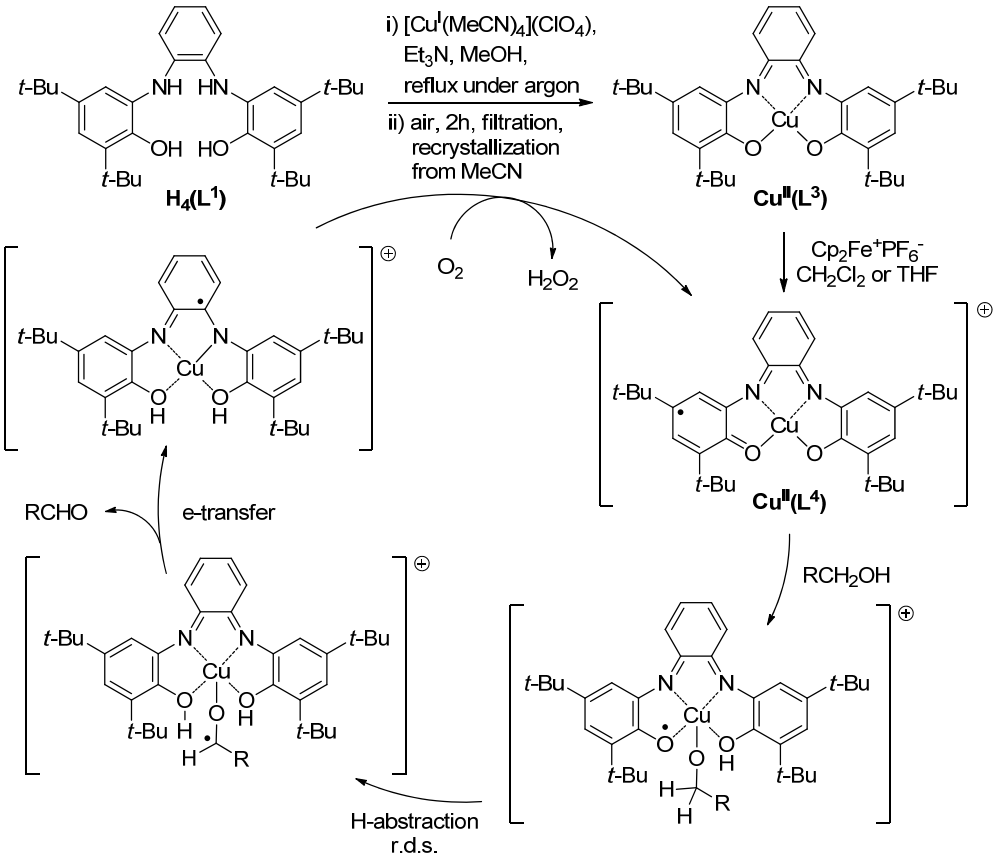
In 1998 Stack and co-workers reported a highly active GO mimetic (**Cu^{II}BSP**) whose active site had similar features as the natural enzyme (Scheme 91).[146] The structural core is derived from the axially chiral BINAM moiety forcing the copper center to adopt a non-planar coordination geometry. The authors verified the tetrahedral coordination by obtaining an x-ray crystal structure of **Cu^{II}BSP**. Other features similar to galactose

oxidase are the phenolic groups with *ortho*-thioether substituents, which indeed were able to effectively stabilize radicals. The active catalyst could be generated from non-ionic **Cu^{II}BSP** by single-electron oxidation or by using ionic Cu(I)BSP$^-$Bu$_4$N$^+$, which gave an equally active catalyst when exposed to oxygen. They also reported that non-ionic **Cu^{II}BSP** itself is fully functional and can form the active form of the catalyst although the initial reaction rate is a lot slower. Eventually **Cu^{II}BSP** leads to similar turnover numbers (TON) compared to those of preactivated catalysts. This catalyst was able to oxidize benzyl alcohol at room temperature with TON of 1300 (over 20 h) when the reaction was carried in neat alcohol. Other activated alcohols such as cinnamyl alcohol and 1-phenylethanol could also be oxidized to the corresponding carbonyl compounds. Primary and secondary alkyl alcohols were not oxidized. Stack and co-workers reported their catalyst to give a 2e$^-$ oxidation process with a mechanism identical to that of galactose oxidase. Although they could not observe the intermediate [Cu(II)BSP(OOH)]$^\bullet$ nor spectroscopicly determine the quantitity of H_2O_2, they justified the 2e$^-$ oxidation process by observing oxygen consumption relative to the produced aldehyde and found this ratio to be 1:1. Kinetic isotopic effect for α-protons ($PhCH_2O^-/PhCD_2O^-$) was found to be k_H/k_D = 5.3, which was similar to that of GO (k_H/k_D = 7.00±0.09, for $PhCH_2OH/PhCD_2OH$).[147] They also observed the Hammett ρ value of -0.14 for *p*-subtituted benzyl alcohols, which was also in agreement with the Hammett ρ value of -0.093±0.32 for GO.[147]



Scheme 91. Galactose oxidase mimic reported by Stack and co-workers in 1998.[146]

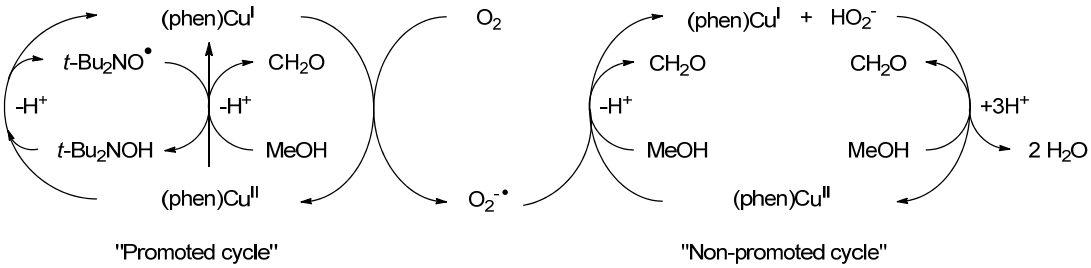
Wieghardt and co-workers reported an exceptionally active GO mimetic in 1999.[148] They synthesized the ligand $\mathbf{H_4(L^1)}$ (Scheme 92) which could be converted to a stable copper(II) complex by complexing the ligand with copper(I) and exposing it to oxygen. In this process the ligand itself underwent a $2e^-$ oxidation to the new ligand H_2L^3, and copper(I) was oxidised to copper(II). A combined $3e^-$ oxidation process gave a new stable complex $\mathbf{Cu^{II}(L^3)}$ in 49% yield. They also obtained an x-ray crystal structure of this complex, which verified the square planar structure. $\mathbf{Cu^{II}(L^3)}$ showed exceptional redox capabilities on voltametric studies and five different oxidation states were observed. These results were an indication of ligand centered redox process. $\mathbf{Cu^{II}(L^3)}$ was found to be inactive in alcohol oxidation and required one-electron oxidation with $Cp_2Fe^+PF_6^-$ in order to form the active catalyst $\mathbf{Cu^{II}(L^4)}$. This catalyst was able to oxidise ethanol to acetaldehyde with an impressive TON of ~4500 (over 50 h, 55% conversion) using air as the terminal oxidant. Production of H_2O_2 was determined spectrophotometrically as a peroxotitanyl species, and was found to be stoichiometrically identical with the production of acetaldehyde. According to the authors, the mechanism is similar to that of GO except that the redox process occurs on the ligand.



Scheme 92. Galactose oxidase mimic reported by Wieghardt and co-workers in 1999.[148]

4.1.2 Copper catalyzed alcohol oxidation mediated by nitroxyl radicals

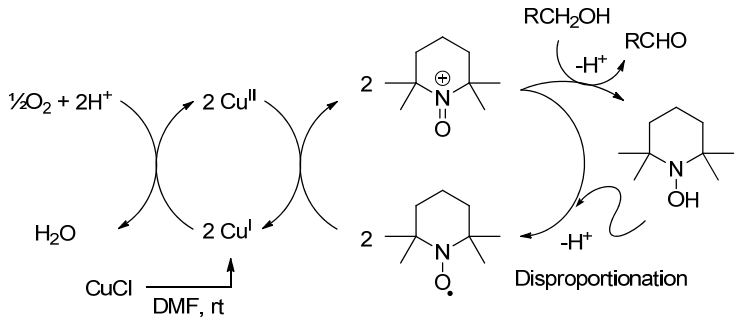
One of the systems currently considered to be a GO mimic is the copper-nitroxyl radical catalyzed oxidation first introduced by Brackman and Gaasbeek in 1966.[149] They described a di-*tert*-butylnitroxyl radical-promoted copper(II) catalyzed oxidation of methanol in a series of three consequative articles. The radical promoter is expected to abstract an α-hydrogen from the methanol coordinated to copper(II) phenanthroline complex (Scheme 93). This process will also reduce copper(II) to copper(I) in a similar process as found for GO. The radical promoter is reoxidized by copper giving another (phen)Cu^{I} species. These copper(I) species are reoxidized by molecular oxygen producing a superoxide radical, which is reduced to water in another reaction cycle. A non-promoted reaction was also found to oxidize methanol to formaldehyde and formic acid, but in a slower reaction rate.



Scheme 93. The first nitroxyl radical promoted aerobic oxidation of alcohols reported by Brackman and Gaasbeek in 1966.[149]

Somewhat later Semmelhack *et al.* showed copper-TEMPO to be an efficient catalytic system in alcohol oxidation under aerobic conditions.[150] They showed that a catalytic system consisting of 10 mol % of CuCl and 10 mol % TEMPO can oxidize various benzylic and allylic alcohols to their corresponding carbonyl compounds in good yields (85-100%). Non-activated alcohols required the use of stoichiometric amounts of $CuCl_2$ and CaH_2. The role of TEMPO was to form a nitrosonium ion by one-electron oxidation with copper(II) (Scheme 94). The corresponding nitrosonium ion is capable of oxidizing the substrate alcohols, as shown by a reaction developed by Cella *et al.* in 1975.[151] A similar observation was published by Ganem only a month later.[152] This reaction was futher developed by others and was later named the Anelli oxidation.[153,137] Regeneration of the TEMPO radical occurs *via* disproportionation of TEMPOH and another

nitrosonium ion. Copper itself acts as a mediator in the oxidation with gaseous oxygen, producing water as a side product.

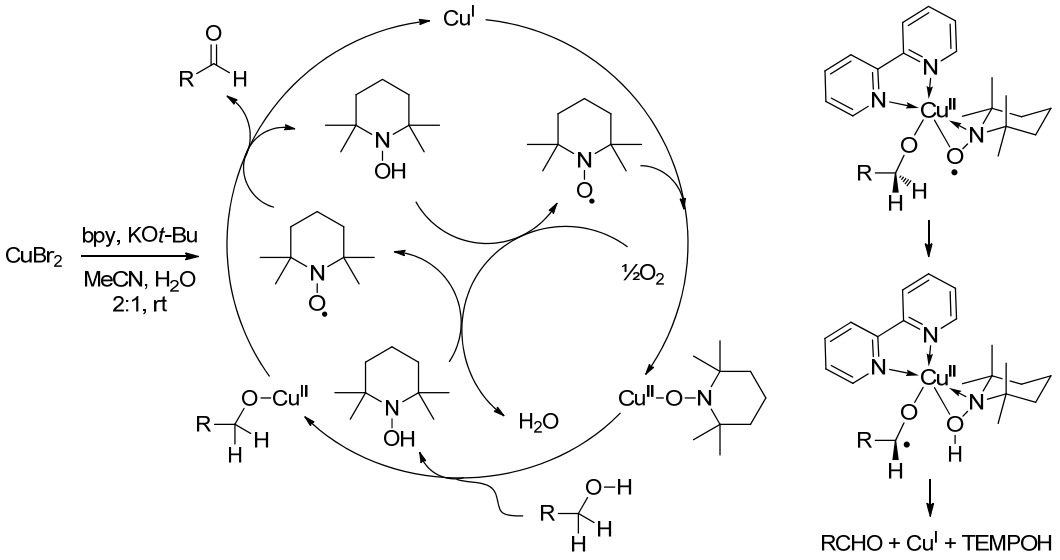


Scheme 94. A mechanism postulated by Semmelhack *et al.* in 1984.[150]

Sheldon and co-workers reported a similar catalytic system in 2003.[154] A major improvement in this new catalytic system was the use of a bipyridine ligand. This modification improved the catalytic efficiency and allowed the use of acetonitrile-water as the reaction medium and air as the terminal oxidant. Benzylic and allylic alcohols could be oxidized in a few hours and the corresponding aldehydes were obtained in excellent yields (91-100%). Aliphatic alcohol (1-octanol) required a prolonged reaction time (24 h). The mechanism was expected to follow the pathway of GO, where TEMPO abstracts an α-hydrogen from the alcohol followed by reduction of Cu^{II} to Cu^{I} (Scheme 95). Major differences are found in the reoxidation steps. TEMPOH is reoxidized by oxygen generating the TEMPO radical and water. Copper(I) is reoxidized by TEMPO generating a copper(II)-TEMPO complex. This is rather surprising since copper is reoxidized by oxygen in the mechanism of GO (Scheme 90) and in the other mechanisms proposed by other research goups (Schemes 93-94).

Sheldon and co-workers made a mechanistic study on their catalytic system where they justified mechanistic details.[154b] Kinetic isotope effect (k_H/k_D) for *p*-Me-benzylic alcohol was found to be 5.42, which is also an indication of substantial C-H bond cleavage in the progress towards the transition stage (Table 6). This value was in agreement with similar values obtained for galactose oxidase, GO mimetic Cu^{II}BSP and $RuCl_2(PPh_3)_3$-TEMPO. Large difference in the kinetic isotope effect between stoichiometric oxoammonium chloride oxidation (k_H/k_D = 1.7-2.3) and Cu-TEMPO system suggested that Semmelhack's mechanism was not correct. A similar value (k_H/k_D = 2.05) was found for Laccase-TEMPO oxidation, which was an indication of an

oxoammonium-mediated reaction. The oxidation of $Cu^{I}OAc$ with TEMPO was analyzed with UV spectroscopy, which showed the formation of Cu^{II} species under inert atmosphere. Sheldon and co-workers also noted that copper(I) is oxidized faster with TEMPO than oxygen. It it unclear how this was determined since no data was given. Aerobic oxidation of TEMPOH was shown by exposing it to air, which led to the appearance of the orange colour of TEMPO.



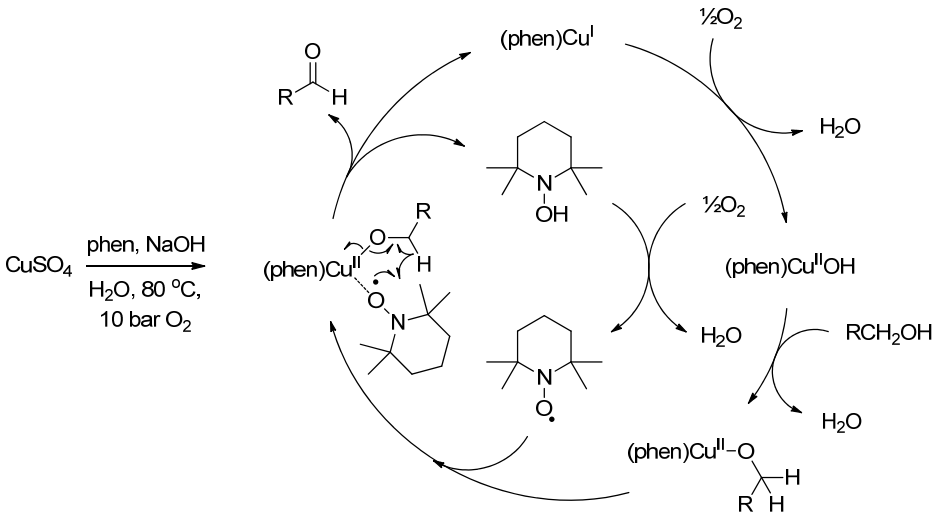
Scheme 95. An alternative mechanism from Sheldon and co-workers.[154]

Table 6. Kinetic isotope effect and Hammett ρ-values for the oxidation of benzyl alcohols.

System	Kinetic isotope effect (k_H/k_D)[a]	Hammett ρ-value	Ref.
CuCl-TEMPO-O_2	5.42	-0.16	154b
Oxoammonium chloride	1.7-2.3	-0.3	155
$RuCl_2(PPh_3)_3$-TEMPO-O_2	5.12	-0.58	156
CuCl-TEMPO-N_2[b]	5.77	-	154b
$[Cu^{II}BSP]$-O_2[c]	5.3	-0.14	146
Galactose oxidase	5.02	-0.09	147
Laccase-TEMPO[d]	2.05	-	157

a) α-D_2-*p*-Me-benzyl alcohol was used. b) TEMPO used as stoichiometric oxidant under nitrogen atmosphere c) α-D_2-benzyl alcohol was used. d) Unknown benzylic alcohol.

In 2007 Repo and co-workers reported a slightly modified mechanism (Scheme 96).[158] Their proposal mainly followed the Sheldon mechanism. A major difference is the reoxidation of copper(I), which is achieved by oxygen and not by TEMPO as in Sheldon's mechanism. Repo and co-workers analyzed the reaction intermediates with high resolution ESI-MS and were able to identify many interesting complexes. Among these were (phen)Cu$(HSO_4)^+$, (phen)$_2$Cu$^+$, (phen)Cu(TEMPO)$^+$, (phen)Cu(BnOH)$^+$. Similar complexes were also indentified with a bipyridyl ligand.



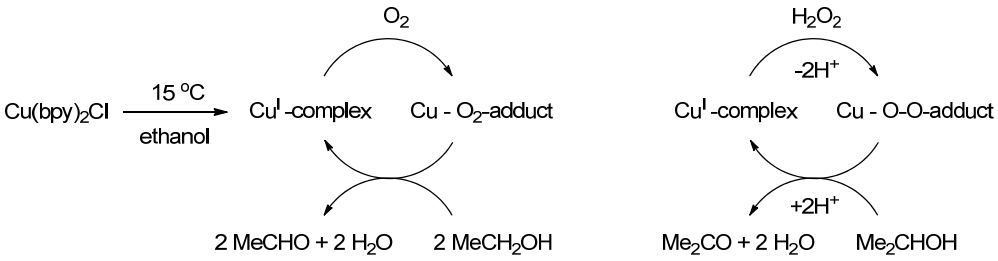
Scheme 96. A modified mechanism reported by Repo and co-workers in 2007.[158]

Below I present some mechanistic alternatives, which differ from each other quite substantially. Some evidence on the catalyst intermediates is given, but do not provide proof for any of the postulated mechanistic alternatives. Although Brackman and Gaasbeek (1966)[149] are usually not recognized for their early findings, the later developments by Semmelhack (1984),[150] Knochel (2000),[159a] Gree (2002)[159b] and Sheldon (2003)[154] have led to ever increasing interest on such catalytic systems.[159]

4.1.3 Other copper catalyzed alcohol oxidations

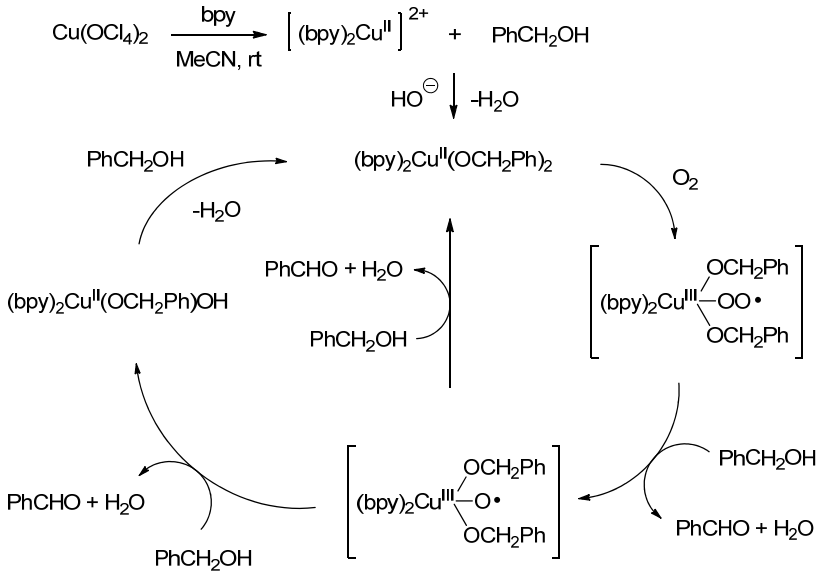
Copper-TEMPO catalyzed oxidations of alcohols have been shown to be very efficient. The mechanism of these oxidations is still unclear, although many variants have been proposed. Some older copper catalyzed alcohol oxidations are functional even without nitroxyl radical mediators. These methods require some attention since they may provide some further information on copper catalyzed oxidations.

In the early 1980 Munakata *et al.* reported a copper(I) catalyzed oxidation of ethanol and few other alcohols under aerobic conditions (Scheme 97).[160] The catalytic cycle of the oxidation of ethanol was described to generate water instead of hydrogen peroxide. This was proven by measuring the quantity of water by Karl Fischer titration. The ratio between acetaldehyde and water was found to be 1:1, which was an indication of a $4e^-$ reduction of oxygen. Hydrogen peroxide was also transformed to water but the yield for acetone was only 75% (with respect to consumed H_2O_2). Some of the hydrogen peroxide might have disproportionated to O_2 and H_2O *via* copper(I) catalysis, which might explain the reduced ratio. Although this system was not very efficient, it has an important role in understanding the catalytic cycle, since Munakata *et al.* provided actual proof for the generation of water in the copper catalyzed alcohol oxidation.



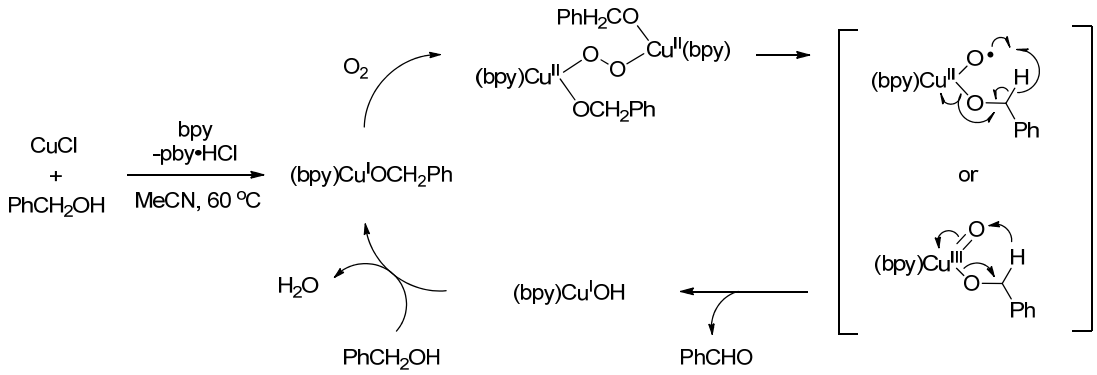
Scheme 97. Copper catalyzed oxidation of ethanol by Munakata *et al.* in 1980.[160]

Sawyer and co-workers described a similar system where $(bpy)_2Cu^{2+}$ is the initial catalyst.[161] Their catalyst system required the use of catalytic amounts of base. This system was able to oxidize benzyl alcohol to benzaldehyde in 37% yield (over 8h). The Sawyer mechanism is extremely complex and has a very strange Cu(III)hydroperoxide radical intermediate. This complex would have 23 valence shell electrons, which makes is even more unbelievable. Also it is not probable that copper(II) is oxidized to copper(III) by oxygen. This hydroperoxide radical is believed to oxidize benzyl alcohol, generating water as the side product. The subsequent copper(III)$O^{\bullet}$ can oxidize another molecule of benzyl alcohol. Although the mechanism is totally unrealistic, this work by Sawyer and co-workers has been the starting point of research by other groups.



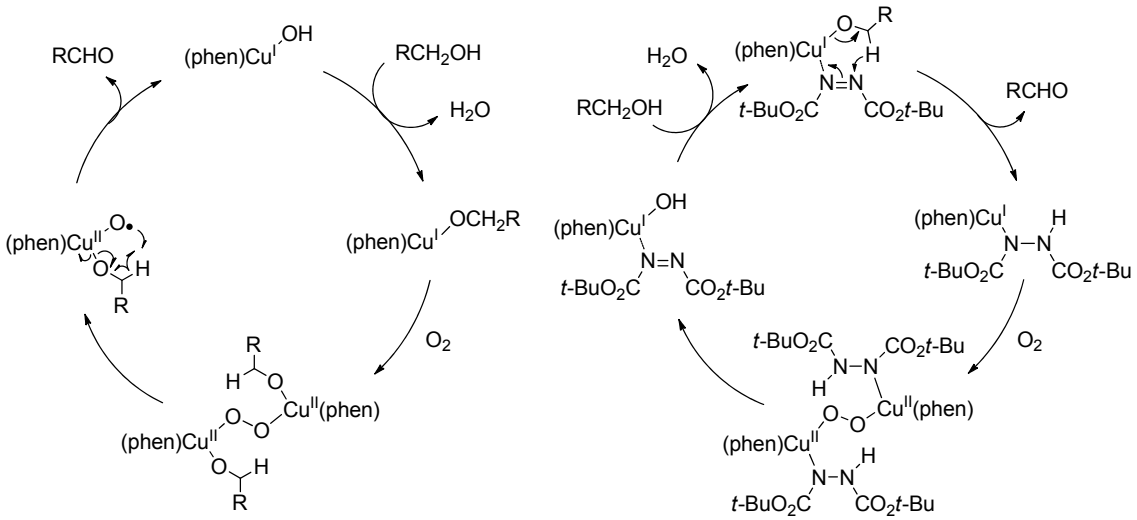
Scheme 98. Copper catalyzed oxidation of benzyl alcohol by Sawyer and co-workers in 1993.[161]

In 1993 Maumy and co-workers reported a more realistic mechanism in a concurrent study (Scheme 99).[162] Their method was able to oxidize diphenylmethanol to benzophenone in 99% yield in only two hours. This method was also functional for the oxidation of primary and secondary benzylic alcohols. The catalyst was generated from 10 mol % CuCl and 1 equivalent of bipyridine in acetonitrile. Smaller amounts of bipyridine led to poorer conversion. The reaction was performed in 60 °C, but was also shown to work at room temperature in a kinetic isotope effect (k_H/k_D = 2.0) experiment of PhCDH(OH). Maumy and co-workers described a mechanism were the oxidation of $(bpy)Cu^{I}OCH_2Ph$ results in a binuclear copper(II) 1,2-μ-peroxo species. This intermediate undergoes peroxide bond homolysis into a radical form, which is able to abstract the α-proton from the alcohol. Alternatively, the radical form can be considered to be a copper(III) oxo species which can oxidize the substrate *via* oxidative rearrangement. Oxidation of the subtrate alcohol reduces copper to $(bpy)Cu^{I}OH$. Ligand exchange with the substrate alcohol produces water as a side product and completes the catalytic cycle.



Scheme 99. A mechanism proposed by Maumy and co-workers in 1993.[162]

In 1996 Markó et al. reported a totally different type of copper catalysis on aerobic oxidation of various alcohols.[163] Their quest for an improved alcohol oxidation with oxygen led them to further investigate some earlier findings from other groups. A catalytic CuCl-phenanthroline (5 mol %) system with stoichiometric amounts of K_2CO_3 showed some promise in alcohol oxidation, but usually led to early catalyst deactivation. The mechanism for this catalytic system was described to be the same as reported earlier by Maumy (Scheme 100). Markó *et al.* postulated that the catalyst deactivation is derived from copper(II) salt formation, which was not able to reenter the reaction cycle. They tested some hydrazine additives which are known to reduce copper(II) to copper(I). Remarkably, these additives were able to enhance the catalyst lifetime and at the same time increase the rate of the reaction.



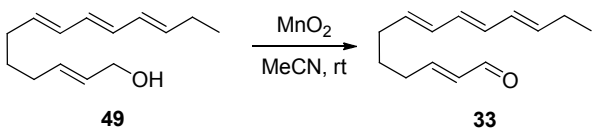
Scheme 100. Azodicarboxylate promoted aerobic oxidations of alcohols reported by Markó *et al.*[163]

A new mechanism was postulated where azodicarboxylate acts as a mediator in an Oppernauer type oxidation (Scheme 100). This oxidation is also known as Mukaiyama oxidation when *t*-BuOMgBr is used as the metal source and 1,1‘-(azodicarbonyl)-dipiperidine as the oxidant.[137] The mechanism involves reoxidation of a copper(I)-hydrazine complex, generating a binuclear copper(II) 1,2-μ-peroxo species. Homolysis of the peroxide bond reoxidizes hydrazine to the azodicarboxylate in combination with the reduction of copper(II) to copper(I). Markó’s catalytic system is one of the most mature aerobic oxidations, and is capable of oxidizing a variety of primary and secondary alcohols. The latest version uses only a catalytic amount of base but still suffers from relatively high reaction temperature (70-80 °C), which detracts from its utility.[163c-d]

Above were described some examples of copper catalyzed alcohol oxidations, which are not promoted by a radical meditor. Similarly, these oxidations are gaining popularity and new variants appear every year.[164]

4.2 Results and discussion

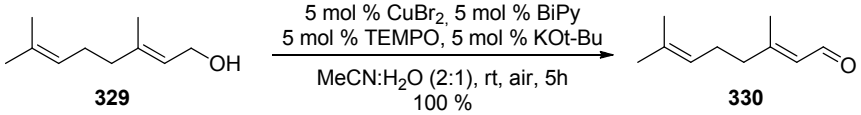
In our quest on a total synthesis of amaminol A, we needed an effective oxidation for the allylic primary alcohol **49** (Scheme 101).[16] Generally such a delicate transformation is usually achieved by using stoichiometric oxidants such as PDC,[137] PCC,[137] activated manganese dioxide,[25,34] Dess-Martin periodinane[36], and IBX.[165] Allylic oxidation can be performed catalytically using the TEMPO-BAIB[166] system, where BAIB acts as the stoichiometric oxidant. Some of these oxidation methods are not particularly sensitive or produce acidic by-products, which in our case would have caused problems. We therefore chose to use the manganese dioxide method. Although the reaction performs well in a small scale, scaling up is problematic due to the high excess of MnO_2 (10-20 eq.) needed.



Scheme 101. Challenging allylic oxidation.[16]

Oxidation of **49** provides a particularly challenging test case, since the product **33** is highly sensitive to excessive heat, light, and both strong Brønsted acids and Lewis acids. In our case, we wanted to subject **33** to an organocatalytic asymmetric intramolecular Diels-Alder reaction. Any background reaction would give a racemic product, thus diminishing the efficiency of the asymmetric synthesis. Any Brønstedt acid produced during the oxidation would be deleterious, and similarly prolonged stirring of the product would also subject the enal to a non-asymmetric process. Therefore, speed is of vital importance for the successful outcome of the oxidation.

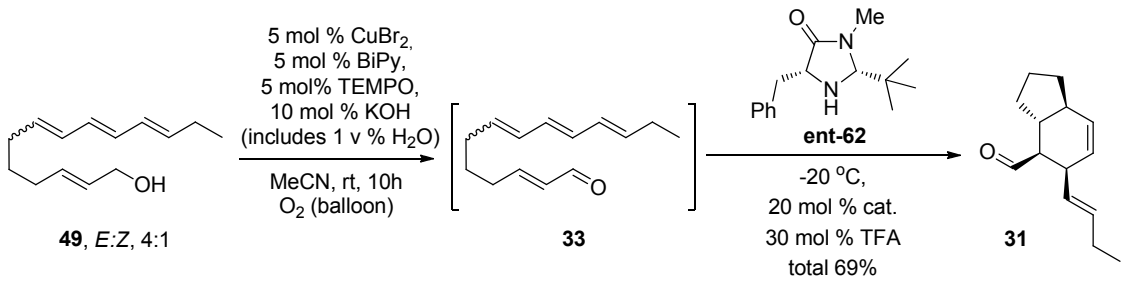
We turned our attention to aerobic oxidations as an alternative method for the allylic oxidation, because these use oxygen as the stoichiometric oxidant and produce water[160] or hydrogen peroxide[148] as by-products. Most of the known aerobic oxidations use harsh conditions with elevated temperatures or high pressures. The copper-TEMPO method described by Sheldon and co-workers seemed the most promising to us (Scheme 102).[154]



329 **330**

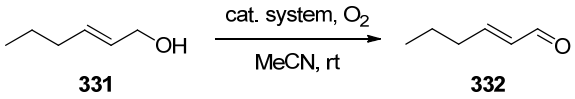
Scheme 102. Sheldon's aerobic oxidation method.[154]

To avoid solubility problems of highly hydrophobic substrates, we initially chose to reduce the amount of water in acetonitrile to 1-2 v % and performed the oxidation of allylic alcohol **49** as described by Sheldon and co-workers. We occasionally obtained a very active catalyst and intermittently almost inactive systems. This poor reproducibility was linked to measurement errors of solid materials in small scale experiments (0.1 mmol of alcohol **49**). The product from one of the successful oxidations of alcohol **49** (2.42 mmol) was subjected to the previously determined (Table 1) IMDA conditions, and aldehyde **31** was obtained in a good yield over two steps (Scheme 103). Although this example gave a promising result, it was still only one reaction out of 28 initial trial oxidations. These trials led to a conclusion that we do not understand the role of the catalyst components on activity, and such detailed information was not given by Sheldon and co-workers.[154]



Scheme 103. Example of initial oxidation studies.

We therefore turned to model experiments using *trans*-2-hexen-1-ol **331** as a simple substrate in order to find the true cause of catalyst inhibition and activation (Scheme 104).[167]



Scheme 104. Model system for allylic oxidation.

Sheldon and co-workers reported that electron rich ligands such as Me-BiPy **335** and MeO-BiPy **334** give a higher reaction rate than bipyridine **333**.[154c] This information led us to try some alternative ligands (Figure 10), since we were aiming at maximizing catalytic activity. We used some bipyridines (**333**, **334**), phenanthrolines (**336**, **337**,[168] **339**[169]**)** and pyridylamine **340** as ligands in the oxidation of the selected alcohol **331**.

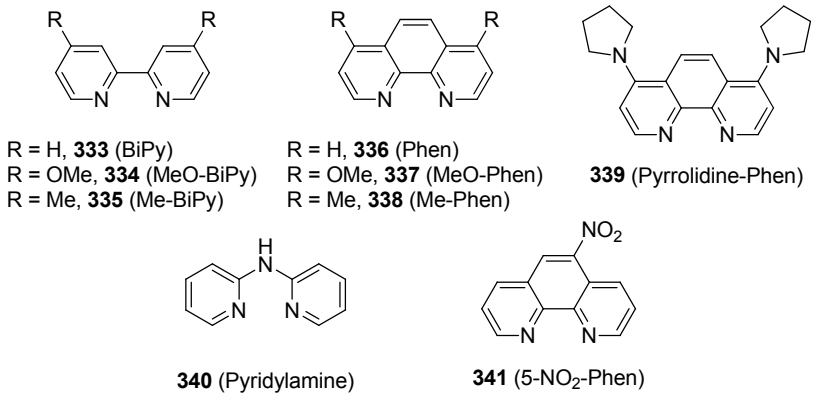


Figure 10. Ligands used by us and Brackman *et al.*[149a] in oxidation studies.

The results were rather surprising, since electron rich ligands MeO-BiPy, MeO-Phen, Pyrrolidine-Phen were found to give slower reaction rates than their unactivated counterparts BiPy and Phen (Figure 11). These results were contradictory to those

reported by Sheldon. Our results followed a trend reported earlier by Brackman and Gaasbeek. They observed relative rates of the reduction of copper(II) to copper(I) with different ligands in the oxidation of methanol with copper using *t*-Bu_2NO• as the radical mediator.[149a] Their relative reaction rates followed an order of 5-NO_2-Phen (2.45) > BiPy (1.75) > Me-BiPy (1.11) > Phen (1.00) > Me-Phen (0.15). It is unclear where this difference comes from, but it may be an indication of a change in progress towards the rate limiting step. We chose to use BiPy according to the following tests, since it gave the highest reaction rate and is a more economical and generally available ligand.

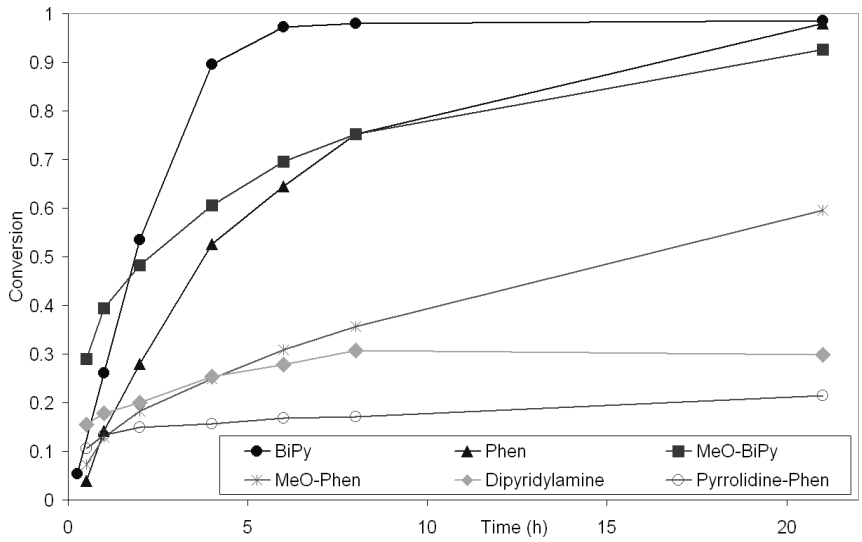


Figure 11. Effect of different ligands in the oxidation of alcohol **331**. Conditions: Alcohol **331** (0.5 mmol), $CuBr_2$ (5 mol %), Ligand (5 mol %), TEMPO (5 mol %), 1 M KOH (10 mol %), 5 mL MeCN, O_2 (balloon).

The effect of different bases on oxidation was examined (Figure 12). In order to minimize measurement errors, we used standard solutions of all the different reaction components. All amine bases were fully soluble in acetonitrile (1 M solution) and therefore no water was introduced into the reaction. Potassium *tert*-butoxide was not soluble enough and was therefore added as a solid. Potassium hydroxide was dissolved in water (1 M solution) and therefore a small amount of water (1-2 v %) was also introduced.

Potassium hydroxide containing reactions gave good reactivity compared to most of the amine bases. The optimal amount of base was investigated using 5-20 mol % of KOH. Slight improvement in the reaction rate was observed when 10 mol % of KOH was used

instead of 5 mol %. Addition of more KOH (marked with arrows in Figure 12) seemed to be detrimental. It was also found that after a few minutes of the addition of KOH some brown solids precipitated (presumably copper hydroxides or oxides). This would decrease the amount of copper in solution and copper-ligand ratios would also be radically influenced. For the rest of the reactions we chose to use 10 mol % of base. Potassium *tert*-butoxide gave a high activity, but it was poorly soluble in acetonitrile.

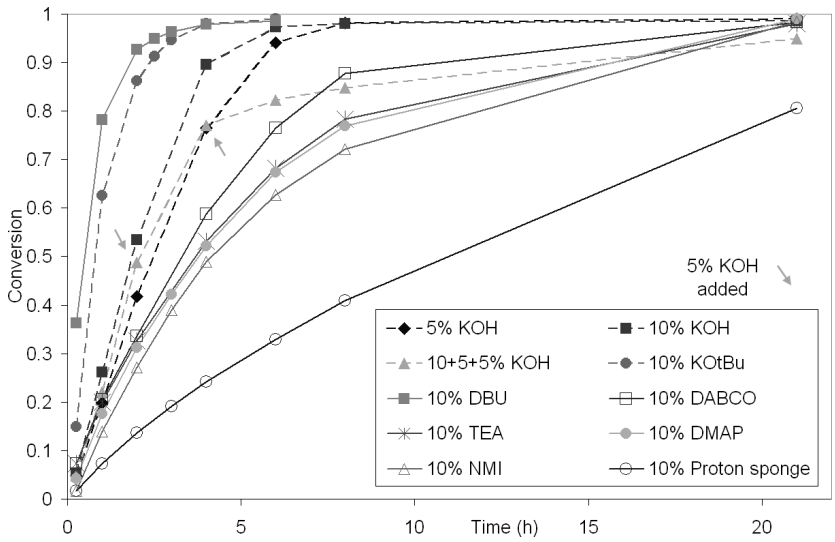


Figure 12. Effect of different bases (in mol %) in the oxidation of alcohol **331**. Solid lines are for amine bases and dashed lines are for potassium containing bases. Conditions: Alcohol **331** (0.5 mmol), $CuBr_2$ (5 mol %), BiPy (5 mol %), TEMPO (5 mol %), 5 mL MeCN, O_2 (balloon).

The activity of the amine bases correlates with their basicities (Figure 12). Proton sponge performed the poorest, and only moderate activities were found for *N*-methyl imidazole (NMI), *N,N*-dimethyl aminopyridine (DMAP) and triethylamine (TEA). 1,4-Diazabicyclo[2.2.2]octane (DABCO) was found to be slightly more active. The highest activity was obtained with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). All reactions with amine bases were homogenous until approximately >95% conversion, when a green precipitation with unknown composition appeared. After this point, the catalyst showed only moderate activity when another equivalent of alcohol **331** was added. Similar deactivation was also reported in the literature.[161]

We now had a reproducible oxidation method where all reaction components could be added as solutions. We then turned our focus on the different catalyst components. First

we decreased the amount of catalyst from 5 mol % to 2 mol % in order to slow the reaction enough to be able to see the differences between the component amounts. We wanted to see whether excess base would also have a detrimental effect when amine bases are used. When the amount of DBU is increased from 4 mol %, a decrease in catalytic activity is indeed observed (Figure 13). This appears even more dramatic when alcohol **331** consumption is plotted onto a second order reaction plot (Figure 14). This plot also shows that the oxidation proceeds with a second order correlation to alcohol concentration. Similar findings have been presented in the literature.[164b]

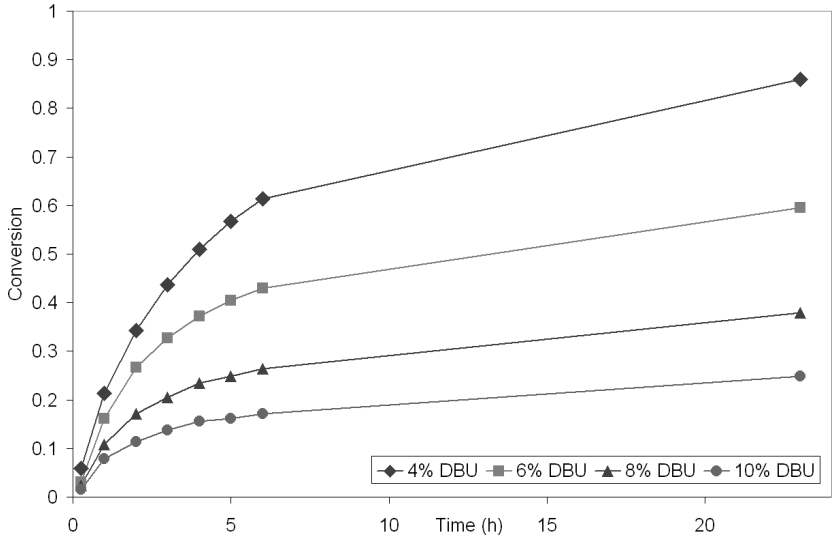


Figure 13. Effect of DBU (in mol %). Conditions: Alcohol **331** (1 mmol), $CuBr_2$ (2 mol %), BiPy (2 mol %), TEMPO (2 mol %), 5 mL MeCN, O_2 (balloon).

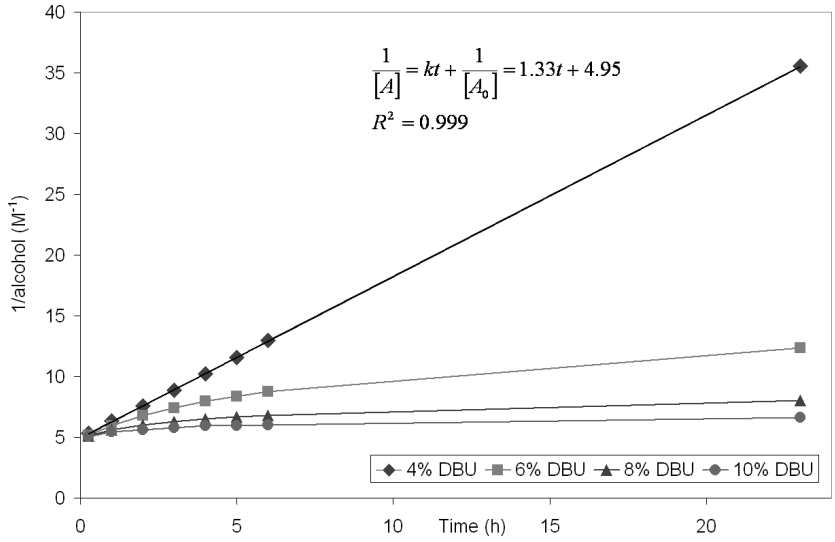


Figure 14. Second order plot (1/[**331**] vs. time) of Figure 13.

Copper catalysts for aerobic oxidations have been shown to have various numbers of nitrogen ligands.[164c] We therefore also investigated the effects of the quantity of 2,2'-bipyridine (BiPy) ligand. When the amount of BiPy was increased from 2 to 4 mol %, the reaction rate slightly increased (Figure 15). Initially it seemed that the amount of ligand does not have a major influence on the reaction. However, within a few hours the reaction started to slow down when 8 or 6 mol % was used in comparison to 2 and 4 mol %. Although 4 mol % was initially faster than 2 mol %, we found that in a prolonged reaction (24h) the reactivity was reversed.

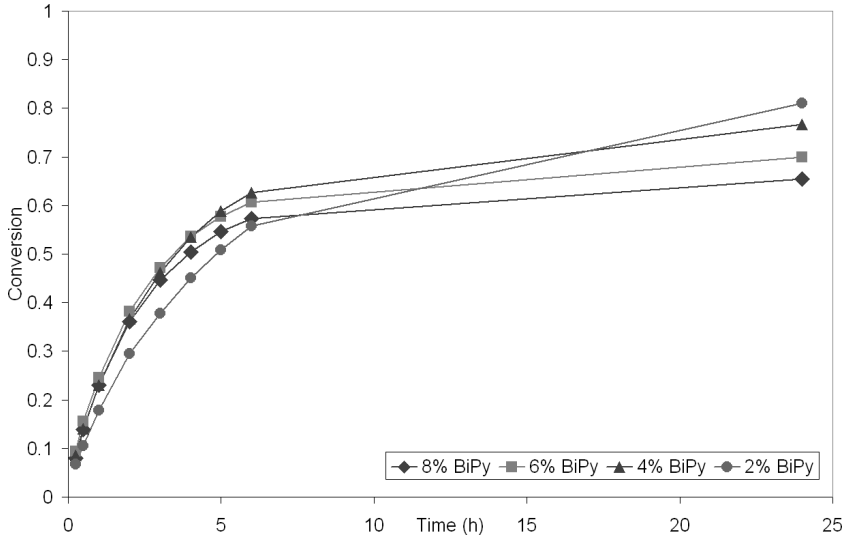


Figure 15. Effect of BiPy (in mol %). Conditions: Alcohol **331** (1 mmol), $CuBr_2$ (2 mol %), TEMPO (2 mol %), DBU (4 mol %), 5 mL MeCN, O_2 (balloon).

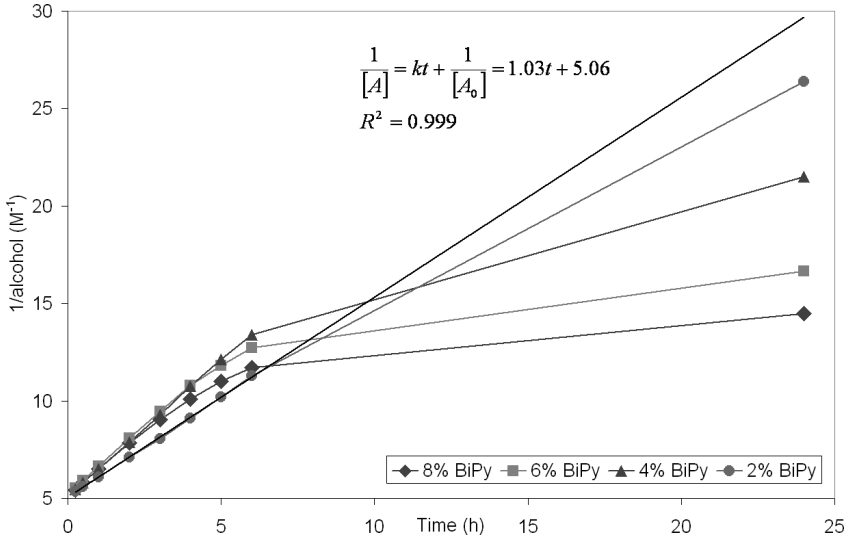
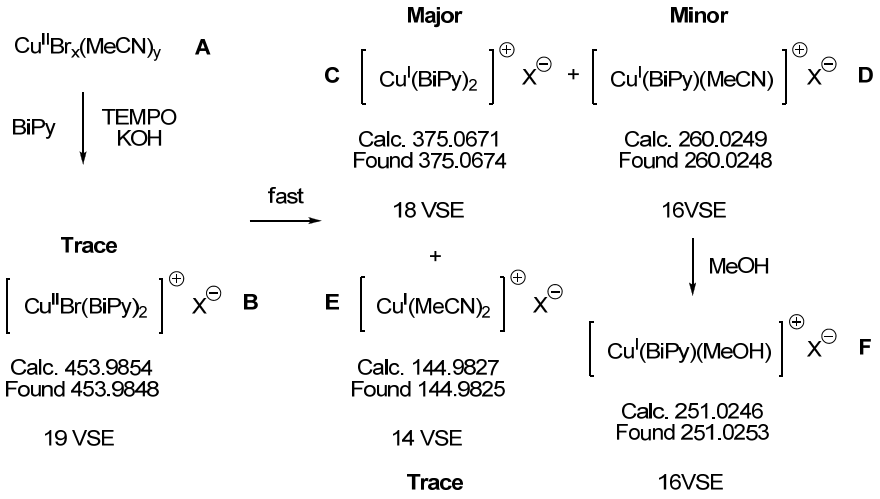


Figure 16. Second order plot (1/[**331**] vs. time) of Figure 15.

The effect becomes clearer when a second order plot is used, although linear fit is not perfect for the whole reaction time (Figure 16). We envisioned that this behaviour is caused by equilibrations. In high dilution copper coordinates easier to one BiPy when more than one equivalent is present in the solution. Eventually more BiPy-ligands coordinate to copper and fill its coordination sphere, thereby deactivating the catalyst.



Scheme 105. Reaction monitoring (35 min after KOH) with HRMS spectrometer.

Further insight was provided by HRMS monitoring of the oxidation experiment with KOH as the base. The solvated form of $CuBr_2$ was rapidly converted to complexes **B**-**E** after BiPy addition (Scheme 105). We were able to identify only a trace of Cu^{II} –species **B**. The majority of copper complexes were rapidly reduced to Cu^{I}. Similar findings have previously been reported using UV-VIS analysis.[164d] The ratio between the major and minor complexes **C**:**D** was approximately 2:1. After two hours the ratio of major components remained the same, but complexes **B** and **E** could not be observed anymore. The major complex **C** has two BiPy-ligands, which fill the coordination sphere of Cu^{I} giving it 18 valence shell electrons (VSE). This complex therefore should be inactive towards reoxidation. The minor complex **D** has only one BiPy and one acetonitrile, filling its coordination sphere only partially with 16 VSE. Such a complex should be able to coordinate to oxygen, which would be followed by reoxidation of copper. After monitoring the reaction for several hours, our HRMS instrument became contaminated with the reaction components. After extensive washing with methanol, the complex **D** was no longer found in the following samples. Complex **D** had lost its acetonitrile ligand, which was replaced by methanol, giving complex **F**. This ligand exchange can also occur in the reaction medium and at the same time influence the

electronic nature of copper, possibly facilitating reoxidation. We also found that when the conversion approaches 100% the catalyst begins to deactivate. We were not able to identify the form of anions in these complexes.

We expect that oxidation follows a pseudo-second order rate law equation (1) where the oxygen concentration can be considered constant.

$$\text{rate} = k[A]^2[O_2] \quad (1)$$

, where k is a function of catalyst (Equation 2).

$$k = k_{cat}[\text{TEMPO}]^a[\text{Cu}]^b \quad (2)$$

Information from the base and ligand quantities indicated that the $CuBr_2$:BiPy:DBU – ratio should be 1:1:2. We chose this ratio for further studies, starting with the influence of TEMPO on the reaction rate. By increasing the amount of TEMPO from 2 to 5 mol % we noticed a clear increase in the reaction rate (Figure 17). A second order plot excluding datapoints at 21 h is shown in Figure 18. Linear fit gave the slopes for different TEMPO amounts. These slopes were then plotted against TEMPO concentrations in a bilogarithmic graph, revealing an approximate first order (1.15) correlation on reaction rate (Figure 19). Similar results have been reported for binuclear copper catalyst.[159g]

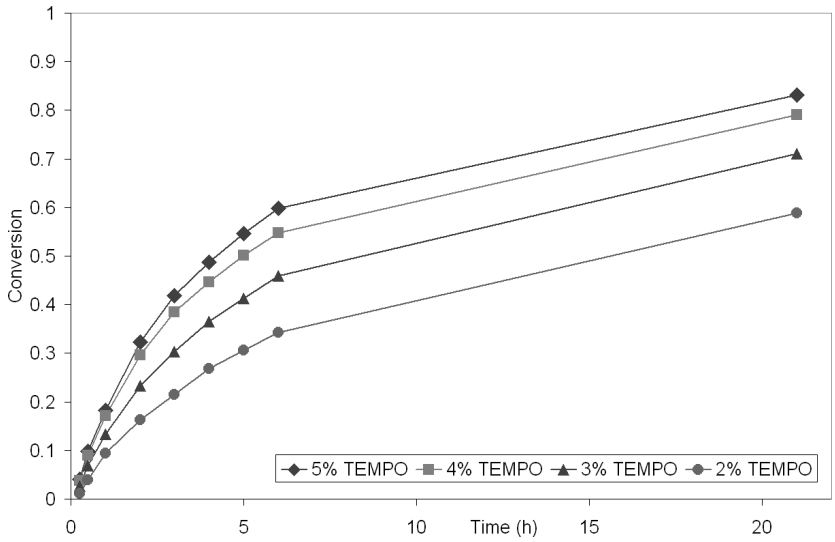


Figure 17. Effect of TEMPO (in mol %). Conditions: Alcohol **331** (1 mmol), $CuBr_2$ (2 mol %), BiPy (2 mol %), DBU (4 mol %), 5 mL MeCN, O_2 (balloon).

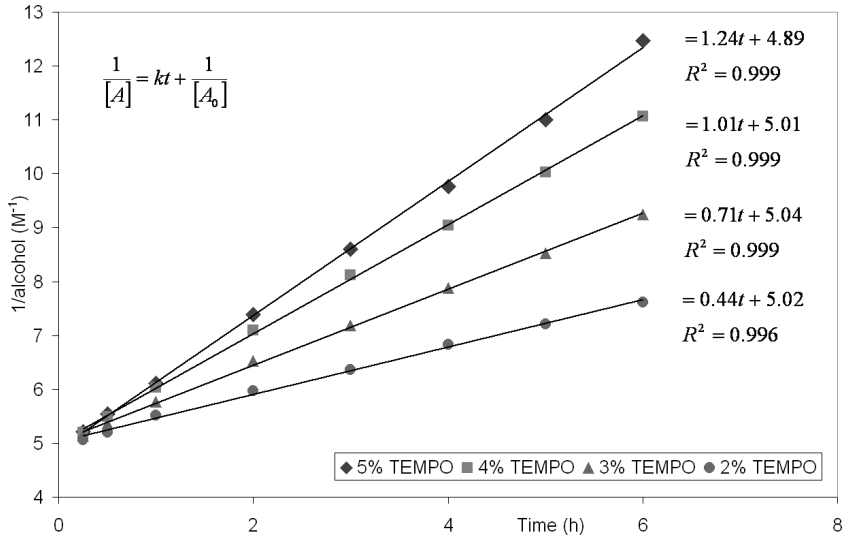


Figure 18. Second order plot (1/[**331**] vs. time) of Figure 17 excluding data points at 21h.

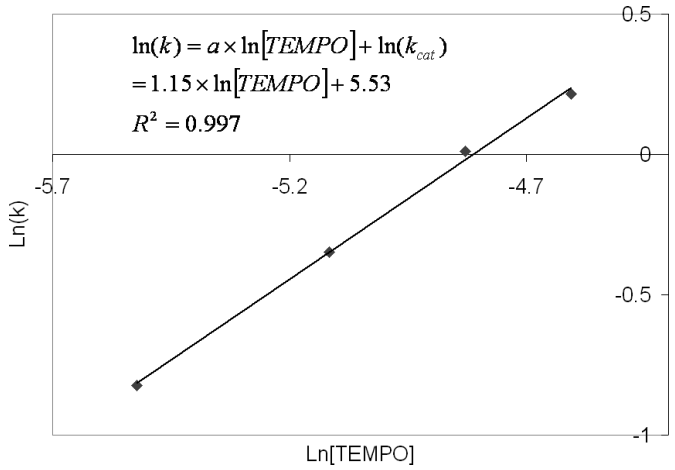


Figure 19. Logarithmic plot (ln(k) vs. ln[TEMPO]) from slopes in Figure 18.

Once we obtained the correlations of DBU, BiPy and TEMPO on the reaction rate, we turned to the most important catalyst species, copper. We chose to use a constant amount of TEMPO (5 mol %) in all experiments and change the quantity of copper keeping the previously determined $CuBr_2$:BiPy:DBU –ratio at 1:1:2. The previously used initial alcohol **331** concentration of 0.2 M was found to be inappropriate, due to high conversions even at 15 min reaction time when larger quantities of copper were used. We therefore lowered the initial alcohol **331** concentration to 0.1 M in order to slow down the reaction.

As expected, increasing the amount of copper dramatically enhanced the reaction rates (Figure 20). We also found that 1 mol % of copper was completely inactive. The reaction medium seemed to have small amounts of impurities which inhibited the reaction. It was assumed that inhibition is also present at higher copper concentrations, but is not as apparent. These reactions did not follow second order correlation in all cases, so the influence of copper was determined using the initial rate method excluding data of the inactive reaction. When the initial rates (5-15 min) were plotted on a logarithmic chart against copper concentration, an approximate second order (2.25) correlation for copper was obtained (Figure 21).

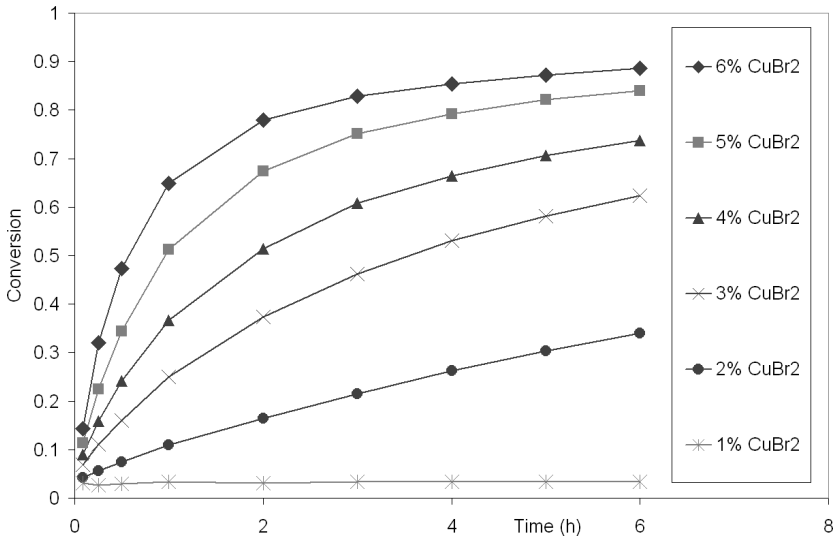


Figure 20. Effect of Copper (in mol %). Conditions: Alcohol **331** (1 mmol), $CuBr_2$:BiPy:DBU (1:1:2), TEMPO (5 mol %), 10 mL MeCN, O_2 (balloon).

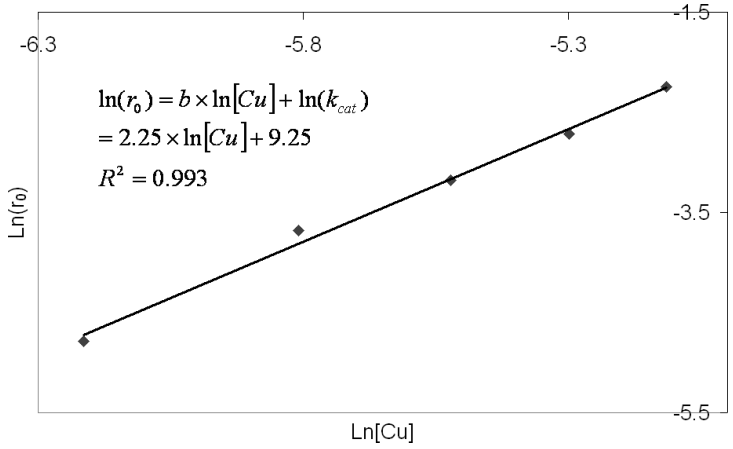


Figure 21. Logarithmic plot ($\ln(r_0)$ vs. ln[Cu]) from initial rates (5 min – 15 min) of Figure 20.

Inhibition of the 1 mol % copper catalysed reaction led us to search for the cause of such behaviour. We found that our unpurified starting material **331** contained some 6% of the aldehyde **332** and 3% of (*E*)-hex-2-enoic acid, as revealed by ^{1}H NMR analysis. Copper(II) acetate has been found to be a poor catalyst in aerobic oxidations.[159n] It is possible that the acid impurity replaces the bromide ligands from the initial copper catalyst, forming a very stable copper complex. The stability of such a complex prevents the TEMPO-initiated reduction to copper(I) species and therefore inhibits the catalytic cycle.

We then performed the catalytic aerobic oxidation using 3 mol % of copper and introducing 3 or 6 mol % of crotonic acid into the reaction (Figure 22). In order to find out if the inhibition is only caused by the increased acidity, we compensated the added acid with an equal amount of DBU in control experiments. As expected, reactions with added crotonic acid lost some of their catalytic activity. Reaction with 6 mol % of crotonic acid was found to be almost completely inactive. Addition of extra base to compensate for the acidic impurities did regain some catalytic activity, although less than in the control experiment. Addition of more DBU will not resolve the carboxylic acid derived deactivation because it also acts as an inhibitor in excessive quantities (Figure 13).

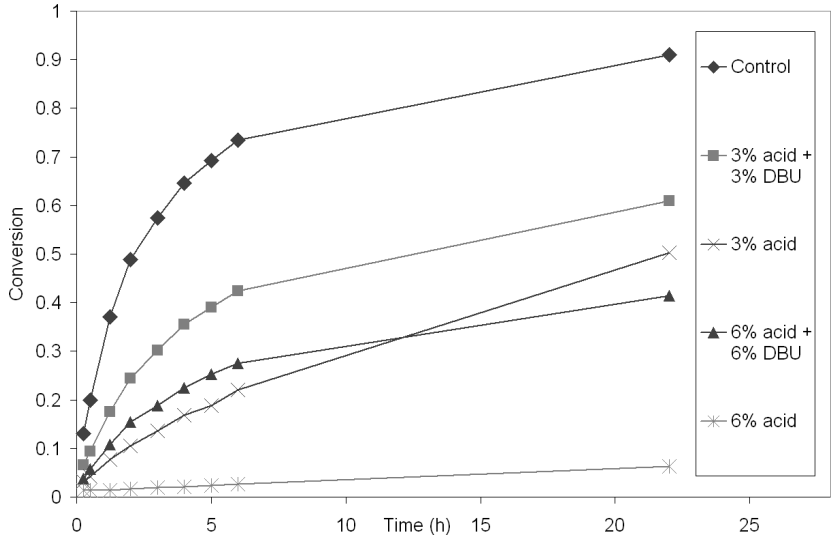


Figure 22. Effect of crotonic acid impurities (in mol %). All reactions: Alcohol **331** (1 mmol), $CuBr_2$ (3 mol %), BiPy (3 mol %), TEMPO (3 mol %), DBU (6 mol %), 5 mL MeCN, O_2 (balloon).

We finally investigated the effect of the alcohol concentration on the reaction rate (Figure 23). Reactions with initial alcohol concentration of 0.2-0.5 M were measured using standard solutions of different reaction components. The most concentrated example with 1.0 M of alcohol **331** in acetonitrile was measured adding the catalyst components as solids. We noticed that when solids are used, there is a need for a premixing time of 10-15 minutes after the addition of copper and bipyridine. This ensures that most of the copper only has one coordinated BiPy-ligand. Otherwise initial reaction rates differed largely, although total reaction times were similar when reactions at this concentration were repeated. As expected, the reactions became faster when performed at higher concentrations. A recent publication on copper-TEMPO oxidations shows that these reactions can also be performed without a solvent.[159o]

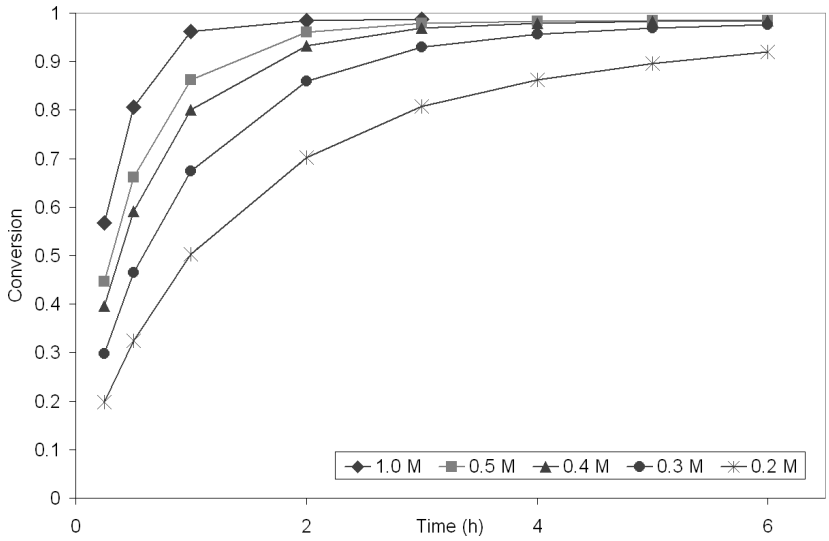


Figure 23. Effect of initial alcohol **331** concentration in acetonitrile. Conditions: Alcohol **331** (1 mmol), $CuBr_2$ (3 mol %), BiPy (3 mol %), TEMPO (3 mol %), DBU (6 mol %), O_2 (balloon).

The use of pure oxygen is not practical when the reactions are scaled up, due to high risk of explosion. We therefore examined the use of air instead of oxygen in order to see if oxygen dissolution is rate limiting at higher reaction concentrations. To minimize measurement errors we used an initial alcohol **331** concentration of 0.5 M, because this was the highest practical concentration for loading reactions using standard solutions. As expected, the reaction with air is slower than with pure oxygen (Figure 24). However, it was interesting to see that the use of air only slightly decreased the reaction rate. Such behaviour is possibly linked to the relatively small scale (1 mmol) used.

Another interesting observation was that reactions with air followed first order kinetics for the whole reaction time (4 h) and the reaction with pure oxygen only for the first 2 hours (Figure 25). This indicates that oxygen becomes a limiting factor for the reaction rate. A similar observation has been made by Kozlowski and co-workers for aerobic copper catalyzed phenolic biaryl coupling, which showed first order dependency on oxygen.[170]

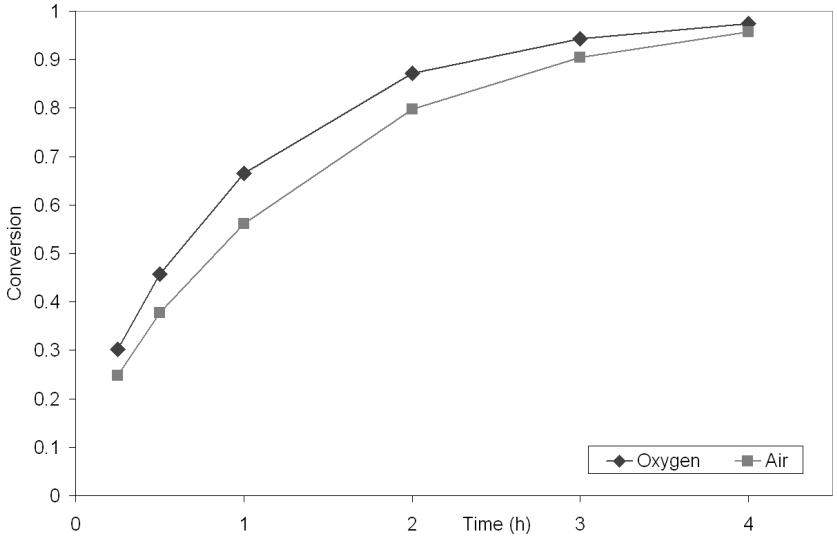


Figure 24. Effect of oxygen source. Conditions: Alcohol **331** (1 mmol), $CuBr_2$ (3 mol %), BiPy (3 mol %), TEMPO (3 mol %), DBU (6 mol %), 2 mL MeCN, O_2 (balloon).

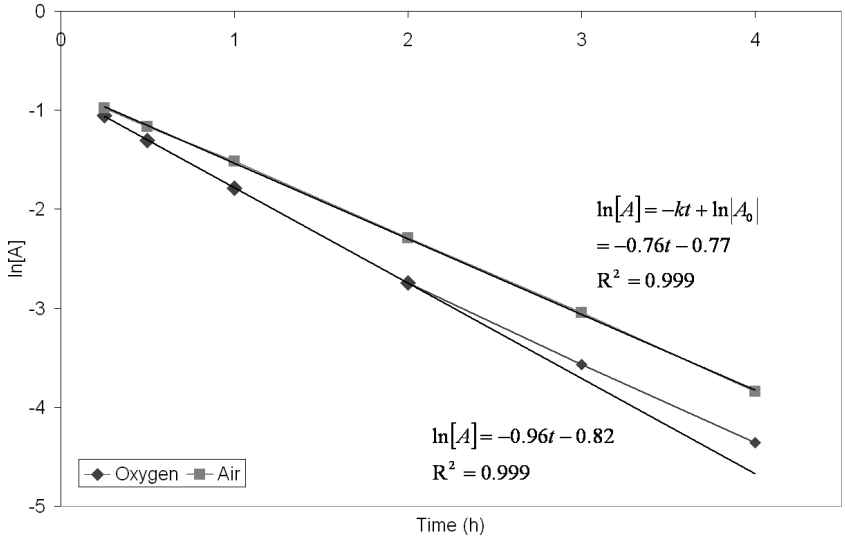


Figure 25. First order plot (ln[**331**] vs. time) of Figure 24.

Interestingly, a fresh bottle of alcohol **331** devoid of any acidic impurities also affected the reactivity. The reaction with DBU failed to reach full conversion. We envisioned that such behaviour is due to the excessively basic conditions, which were previously partially neutralized by acid impurities. The reactivity was regained by changing the base to *N*-methyl imidazole.

We also examined the use of different solvents (Figure 26). Fluorobenzene and pure dichloromethane were found to be almost inactive due to insolubility of the catalyst. Acetonitrile was found to be the most suitable due to good catalyst solubility and reaction rate. The solvent can be partially replaced with dichloromethane although the reaction slows down slightly. Addition of water slightly reduces the reaction rate. This behaviour is most likely caused by competing coordination to the copper catalyst. Addition of *tert*-butanol had no effect on reactivity. Coordination of *tert*-butanol to copper is evidently much less preferred than that of allylic alcohol **331**.

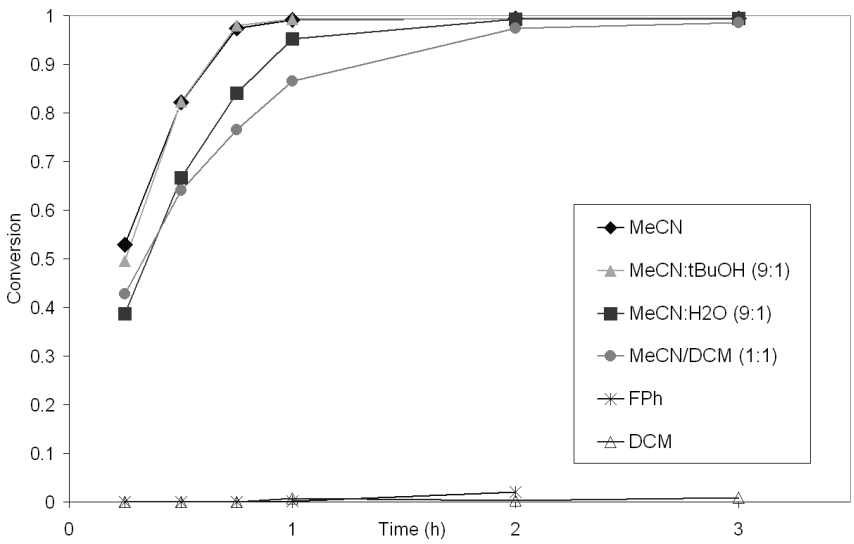
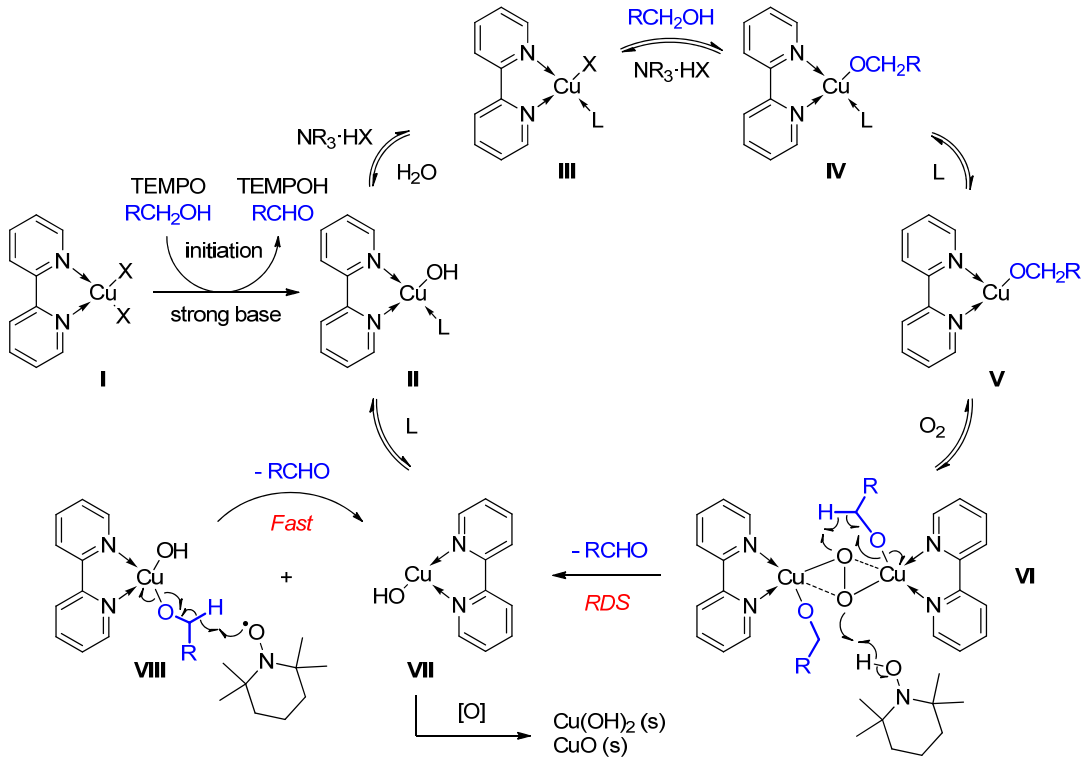


Figure 26. Solvent effect on conversion. Conditions: Alcohol **331** (2 mmol), $CuBr_2$ (3 mol %), BiPy (3 mol %), TEMPO (3 mol %), NMI (6 mol %), 2 mL solvent, O_2 (balloon).

In summary, we found a first order kinetic correlation for TEMPO and a second order correlation for copper. Also the bipyridyl ligand stoichiometry and careful control of basicity are important factors in determining the catalytic activity. The substrate alcohol has a second order and oxygen a first order kinetic dependency.

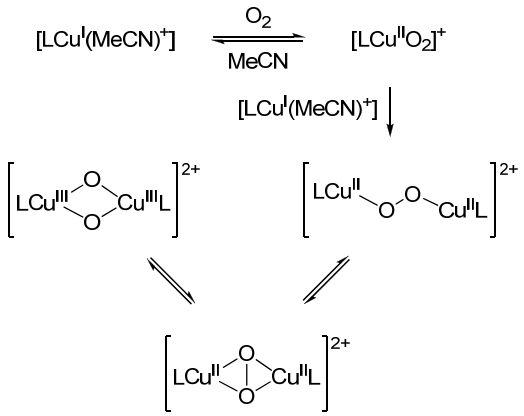
Commonly copper-TEMPO oxidations are represented using a reactive catalytic species postulated by Sheldon and co-workers (Scheme 95).[154] In this complex TEMPO is coordinated to copper in an η^2 manner. This postulation is not supported by our findings, because in such a case copper and TEMPO should have identical kinetic factors. Copper-TEMPO systems are also considered to be monocopper enzyme galactose oxidase (GO) mimetic. Our findings would support a binuclear copper system which is not in agreement with the assumption of GO mimicry.



Scheme 106. Proposed oxidation mechanism. L = ROH, MeCN or NR_3 type neutral σ-donor ligand.

Inspired by the vast literature[171] on oxygen activation using copper complexes combined with our experimental data, we envisioned an alternative mechanism for copper-TEMPO systems (Scheme 106). Copper(II) salt **I** enters the cycle with the help of a strong base and TEMPO, and reduces to copper(I) complex **II** or **III** by oxidation of the substrate alcohol. An equilibration replaces the leaving group X or hydroxide with the alcohol, giving an 18 electron complex **IV**. This species further needs to lose a ligand to give the 16 electron copper(I) complex **V**, which is oxidized by oxygen to a binuclear copper(II) complex **VI**. Such a complex can be formulated as a copper(II) 1,2-μ-peroxo, copper(II) μ-η^2: η^2-peroxo (as presented in Scheme 106) or copper(III)[172]

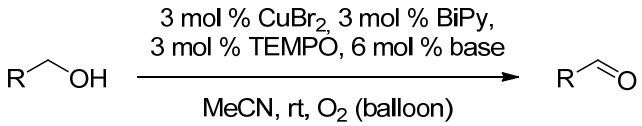
bis(μ-oxo)[173] complex, because these are represented to be in equilibrium and the true nature of the system is unclear (Scheme 107). Once the biscopper complex **VI** meets TEMPOH, the rate determining step (RDS), oxidation of the coordinated alcohol, occurs via radical mechanism, generating TEMPO, along with complexes **VII** and **VIII**. The generated TEMPO oxidizes another molecule of alcohol rapidly with copper(II) complex **VIII**, because only copper(I) species are observed during the course of the reaction. A possible deactivation of the catalytic species can occur when copper hydroxides, such as complex **VII**, become insoluble by forming copper oxides or non-ligated hydroxides.

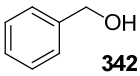
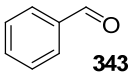
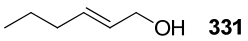
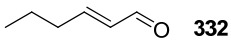
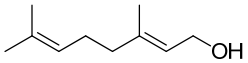
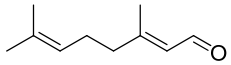
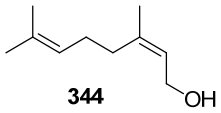
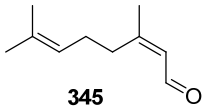
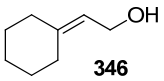
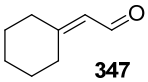
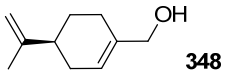
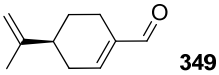
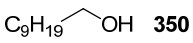
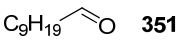


Scheme 107. Equilibria between different copper oxygen complexes.

After optimizing the reaction conditions, we wanted to test the scope and limitations of the method on oxidation of various alcohols (Table 7). Both benzylic and allylic alcohols were converted to the corresponding alcohols at room temperature in good isolated yields (entries 1-8). When DBU was used with geraniol **329**, full conversion could not be obtained due to catalyst deactivation (entry 3). DMAP was able to produce 99% conversion, but a small portion of citral **330** was also isomerized to neral **345** (entry 4). By using NMI a rapid reaction and good isolated yield could be obtained without isomerization of the *E* double bond (entry 5). Such conditions were also tested for the oxidation of nerol **344** which produced neral **345** without isomerization to citral **330** (entry 6). Similarly, isomerization of an exocyclic double bond to an endocyclic one was not observed (entry 7). The slightly more sterically demanding substrate perillyl alcohol **348** was also easily converted to perillaldehyde **349** (entry 8).

Table 7. $CuBr_2$-catalyzed oxidation of alcohols to carbonyl compounds.[a]



Entry	Substrate	Product	Base	Time (h)	Conv. (%)[b]	Yield (%)[c]
1	 **342**	 **343**	DBU	0.7	100	78
2	 **331**	 **332**	NMI	2	99	84
3	 **329**	 **330**	DBU	2	73[d]	-
4			DMAP	2	99	-
5			NMI	1	99	94
6	 **344**	 **345**	NMI	2	99	93
7[e]	 **346**	 **347**	NMI	0.5	99	86
8	 **348**	 **349**	NMI	1.5	99	94
9	 **350**	 **351**	DBU	0.5	17[d]	-
10			NMI	3	NR[f]	-
11			NMI/DBU[g]	20	49	-
12			NMI[h]	20	87	-

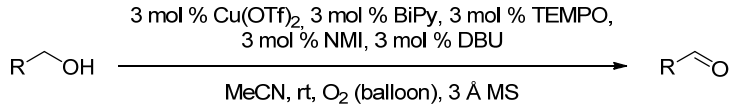
a) Conditions: Alcohol (10 mmol), $CuBr_2$ (3 mol %), BiPy (3 mol %), TEMPO (3 mol %), base (6 mol %), 10 mL MeCN, O_2 (balloon), room temperature. b) Conversion determined with GC. c) Isolated yield of analytically pure material. d) No significant activity was observed after specified time. e) Done with 5 mmol of alcohol. f) No reaction. g) Both bases 3 mol %. h) CuBr (3 mol %), BiPy (3 mol %), TEMPO (3 mol %), NMI (3 mol %) was used.

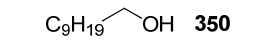
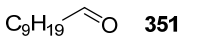
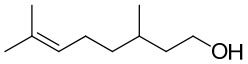
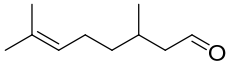
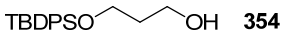
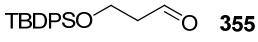
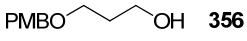
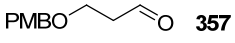
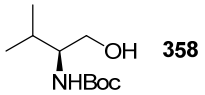
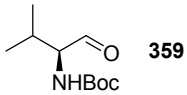
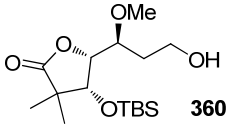
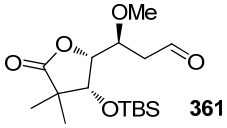
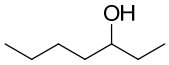
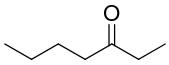
The catalyst system was also tested for 1-decanol **350** (Table 7, entries 9-12). When DBU was used as the base, only a small amount of decanal **351** was obtained (entry 9). As previously noted, excessively basic conditions result in premature catalyst deactivation. When the base was changed to NMI we could not obtain any reactivity (entry 10). It seems that a strong base is needed to initiate the reduction to copper(I) species. When combining the beneficial effect of DBU as a strong base and the

selectivity of NMI as a weak base, we obtained rapid conversion to 35% after which the reaction rate diminished due to catalyst precipitation out of the reaction medium (entry 11). After 20 hours only a 49% conversion was obtained. In order to prove our hypothesis on the strong base effect in initiation, we chose to use copper(I) bromide in an experiment with only NMI as base (entry 12). Rapid conversion to 51% was achieved in 30 minutes, after which major loss of catalytic activity was observed, also due to catalyst solidifying. After 20 hours we obtained 87% conversion. Although higher conversion could be obtained using copper(I) bromide, the poor catalyst solubility after some reaction cycles could not be resolved.

We turned our attention to the copper counter ions. We envisioned that the ammonium salts (NR_3•HX) which are formed in the initiation, could influence the copper hydroxide intermediates by trapping them and forming the corresponding copper salts (Scheme 106). By changing the copper source to $Cu(OTf)_2$ we were able to oxidize 1-decanol **350** to almost full conversion (98%) without copper precipitating out of the solution (Table 8, entry 1). We postulated that the water generated in the reaction might have two detrimental effects. Water competes with the substrate alcohol in the coordination to catalyst, and it can also form hydrates from the product aldehyde, which would eventually lead to over-oxidation once the alcohol concentration decreases. In the presence of molecular sieves 1-decanol **350** was oxidized with complete conversion in three hours in excellent isolated yield (entry 2). In a small scale (0.2 mmol) experiment using 5 mol % of catalyst, the reaction time was reduced to only one hour (entry 3). Citronellol **352** was also rapidly converted to citronellal **353** (entry 4). Partially protected 1,3-diols can be oxidized to aldehydes without elimination, but complete conversion could not be obtained (entries 5-6). Protected valinol **358** was also converted to aldehyde **359** in good conversion (entry 7). Unfortunately, enantiopurity of the fragile α-stereocenter dropped from 97% ee to 40% ee. The complex substrate **360** with an exceptionally easily eliminating methoxy functionality can be converted to the corresponding aldehyde **361** without elimination (entry 8). Even secondary alcohols are oxidized to ketones, but elevated temperature of 40 °C and long reaction time (48 h) are needed (entry 9).

Table 8. $Cu(OTf)_2$-catalyzed oxidation of alcohols into carbonyl compounds.[a]



Entry	Substrate	Product	Time (h)	Conversion (%)[b]	Yield (%)[c]
1	 **350**	 **351**	5	98[d]	-
2			3	100	95
3[e]			1	100	-
4	 **352**	 **353**	2	100	91
5	 **354**	 **355**	4	84[f]	76
6	 **356**	 **357**	3	87[f]	55
7	 **358**	 **359**	4	95	82
8[g]	 **360**	 **361**	3	90	65
9[h]	 **362**	 **363**	48	59	-

a) Conditions: Alcohol (10 mmol), $Cu(OTf)_2$ (3 mol %), BiPy (3 mol %), TEMPO (3 mol %), NMI (3 mol %), DBU (3 mol %), 10 mL MeCN, 3 Å molecular sieves, O_2 (balloon), room temperature. b) Determined with GC. c) Isolated yield of analytically pure material. d) Without 3 Å molecular sieves. e) Done with 5 mol % of all catalyst components and 0.2 mmol of alcohol in 0.5mL of MeCN. f) No significant activity was observed after specified time. g) As entry 3 but with 0.23 mmol of alcohol, conversion estimated from crude ^{1}H NMR. h) Reaction carried at 40 °C.

The change of copper source to copper(II) triflate fundamentally changed the catalytic system. We obtained a more active catalyst with a prolonged catalyst lifetime when comparing to copper(II) bromide. This fundamental difference required a new investigation on the reaction medium, since copper(II) triflate is more soluble in a variety of solvents. We tested a few solvents and found out that acetonitrile was still the most suitable solvent for these aerobic oxidations (Figure 27). To our surprise,

dichloromethane and fluorobenzene, which previously were found to be inactive with $CuBr_2$, also showed active reactions. Other solvents were less suitable due to premature catalyst inactivation.

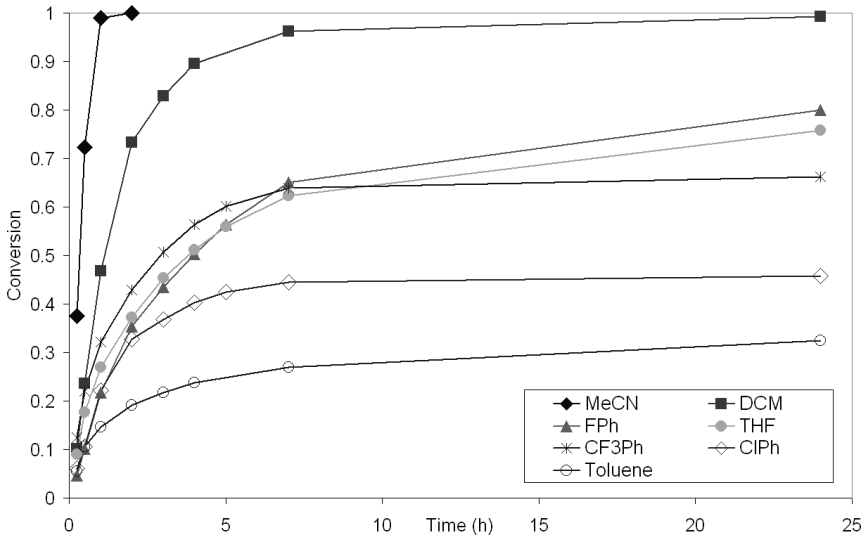


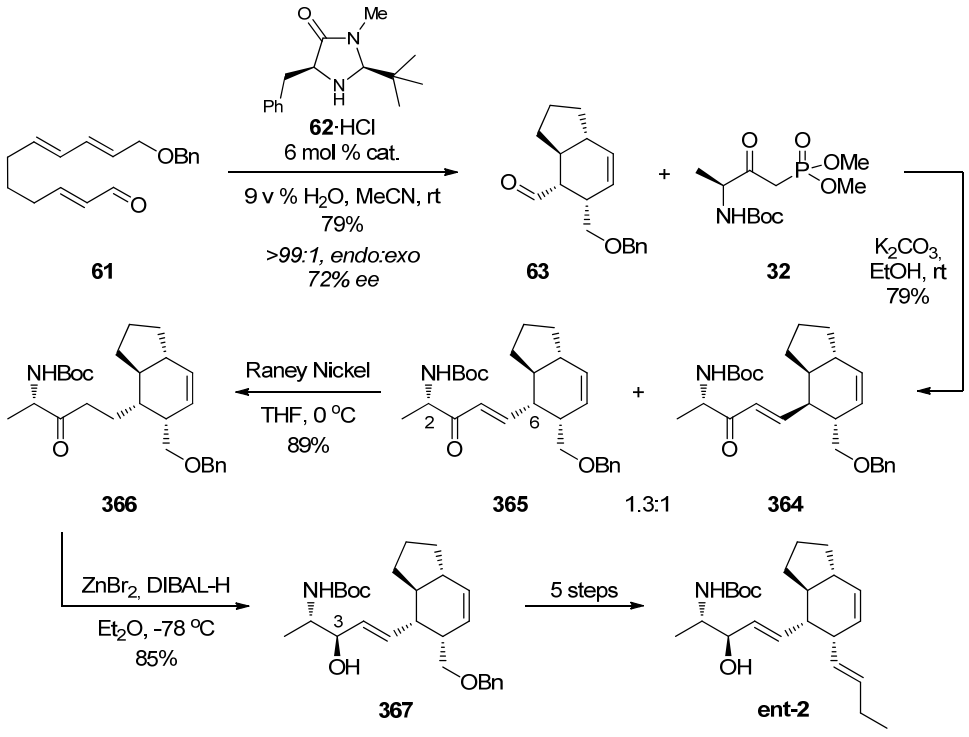
Figure 27. Solvent effect on conversion. Conditions: 1-Decanol **350** (5 mmol), $Cu(OTf)_2$ (3 mol %), BiPy (3 mol %), TEMPO (3 mol %), NMI (3 mol %), DBU (3 mol %), 5 mL solvent, 4 Å molecular sieves (1.0 g), O_2 (balloon).

4.3 Conclusions

In conclusion, the effect of catalyst components in aerobic copper-TEMPO oxidations of alcohols to carbonyls compounds was studied. The amount of base is critical for the outcome of the oxidation. Stoichiometric amounts of copper and BiPy should be used to ensure good activity. We found a 1.15 order kinetic correlation for TEMPO and a 2.25 order correlation for copper. We also found that these oxidations follow a second order dependency on the substrate alcohol at low concentrations and first order dependency on oxygen at high alcohol concentrations. Higher alcohols concentrations are more beneficial for the reaction rate and prevent premature catalyst deactivation. Copper(II) bromide based system was found to be a fast and mild method for allylic alcohol oxidations. A catalytic system based on copper(II) trifluoromethanesulfonate was suitable for more challenging alcohol substrates, although the cause of the difference could not be fully elucidated. This method is clearly more active than previously described ones and further studies are warranted to elucidate its full potential.

5 TOTAL SYNTHESIS OF AMAMINOL B

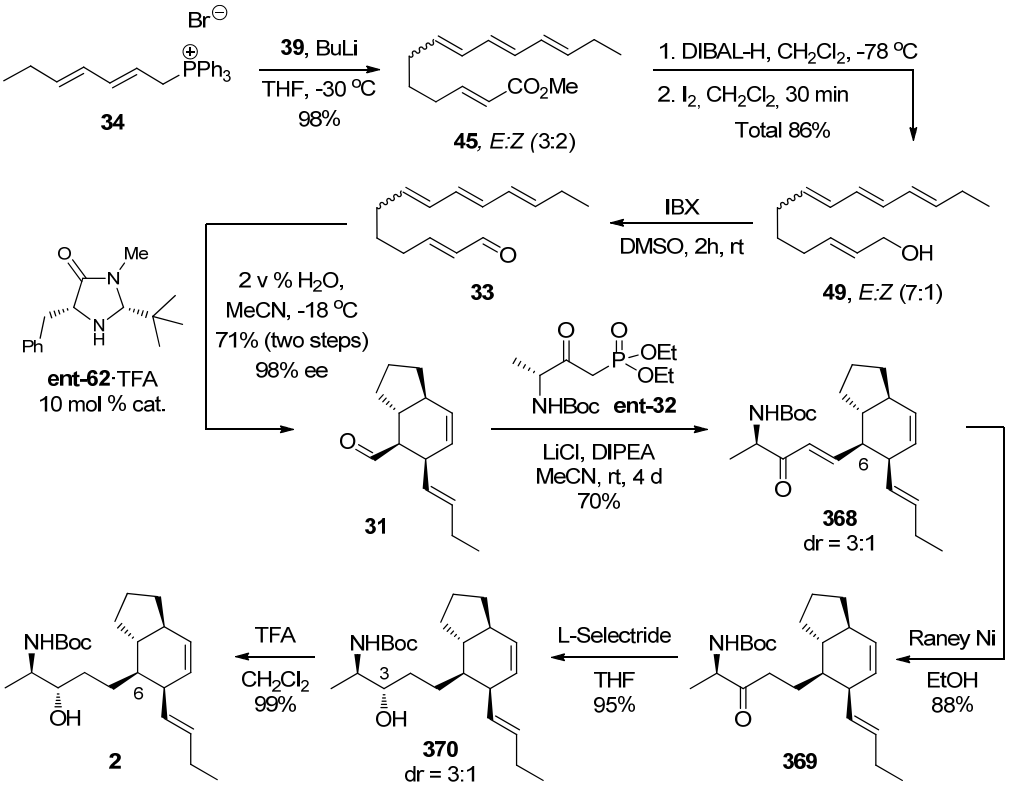
During the course of this work I realized that my former instructor Sami Selkälä had described the total synthesis of enantiomer of amaminol B **ent-2** in his doctoral thesis in 2003.[25] He constructed the hexahydroindene core **63** with an organocatalytic intramolecular Diels-Alder reaction. Side chain was attached with a HWE-reaction of phosphonate **32** by using potassium carbonate in ethanol. These conditions led to epimerization of the C6 stereocenter and gave a mixture of enones **365** and **364** in 1.3:1 –ratio. Fortunately these isomers could be separated with flash chromatography. Enone **365** was reduced with stoichiometric amounts of freshly made Raney Nickel to the corresponding ketone **366**. This ketone was reduced with DIBAL-H in the presence of $ZnBr_2$ to give the *2S,3R* –stereochemistry of **367**. This stereochemical outcome was originally (in the thesis) analyzed to be *2S,3S* due to poor interpretation of Cram's chelation model. Further synthesis over 5 steps gave enantiomer of amaminol B **ent-2**.



Scheme 108. Synthesis of enenantiomer of amaminol B **ent-2**.[25]

Selkälä could not match the spectral data of the end compound to those of isolated natural amaminols A and B, and therefore could not provide proof of the total synthesis. I also had similar problems in my total synthesis of amaminol A **1** (Section 2.5). I later realized that natural amaminols have been isolated as TFA-salts which have an influence on the spectral data. After this observation I was able to prove that I did indeed had synthesized amaminol A **1**.

Jacobs and Christmann reported the first total synthesis of amaminol B **2** in 2008.[165] Their synthesis route was found to be identical to that we described for amaminol A.[16] This is not surprising since they adopted the synthesis strategy for late stages from Selkälä's doctoral thesis after failing in a different approach. Unfortunately, their synthesis suffers from same problems found in Selkälä's thesis. Epimerization of the C6 stereocenter was observed in a HWE-reaction when using the Masamune-Roush conditions. A second problem is in the reduction of conjugated enone **368** since freshly prepared Raney nickel is not the most practical way of making this conversion. These two problematic steps were the ones I was determined to improve in the synthesis of amaminol A **1**.



Scheme 109. First total synthesis of amaminol B **2**.[165]

6 CONCLUSIONS

The aim of this work was to develop a synthesis route for amaminols A **1** and B **2**. Our previous work[25] on the total synthesis of amaminols revealed some problematic reactions, which needed to be improved. A secondary aim was to synthesize enough material for biological activity studies, since the source of amaminols is an unindentified tunicate and therefore unknown.

These goals were achieved, and we were able to report the first total synthesis of amaminol A **1** in 12 linear steps with an overall yield of 20% starting from cyclopentene. The synthesis produced 51 mg of amaminol A **1**, whose biological activity was analyzed at the National Cancer Institute. During the synthesis we developed improved methodologies for the problematic HWE-reaction and conjugate reactions of enones using copper hydrides. Methodology on copper hydrides was futher studied and we were able to develop a highly selective catalytic system for reduction of enones with α-chiral stereocenters. We also discovered that natural amaminols have been isolated as their corresponding trifluoroacetic acid salt.

The oxidation of vulnerable allylic alcohols were more difficult than expected. Problems in scale up led us to research the aerobic oxidation of allylic alcohols. After initial studies done in the amaminol synthesis route, we chose to do a more detailed study on aerobic oxidations catalyzed by copper-TEMPO systems since full understanding of such systems was not available. In this detailed study we discovered that the previously described mechanism is probably incorrect. We proposed a new mechanism which was in agreement with the kinetic data measured for different catalyst components. Copper-TEMPO catalyzed aerobic oxidation of allylic alcohols proved to be a very efficient method and is probably one of the best available methods for this transformation. Aliphatic primary alcohols were more challenging substrates. This methodology still requires some development since the catalyst is deactivated prematurely in these cases.

7 EXPERIMENTAL SECTION

This section consists of experimental details which have not been published in the literature. Copies of the important NMR spectra can be found in the supporting information section of these articles.[16,136,167]

7.1 General experimental

All reactions were carried out under an argon atmosphere in flame-dried glassware, unless otherwise noted. Nonaqueous reagents were transferred under argon *via* syringe or cannula and dried prior to use. THF and ether were distilled from Na/benzophenone, toluene from Na, MeOH from $Mg(OMe)_2$ and CH_2Cl_2 from CaH_2. Alternatively solvents (CH_2Cl_2, THF, ether, MeCN, toluene) were dried by passing deoxygenated solvents through activated alumina columns using MBraun SPS-800 Series solvent purification system. Merck 3 Å molecular sieves were flame dried under high vacuum and kept in oven (120 °C). The concentration of butyl lithium was determined by double titration method using 1,3-diphenyl acetone-*p*-tosyl hydrazone (200 mg) in dry THF (4 ml). Other solvents and reagents were used as obtained from supplier, unless otherwise noted. Analytical TLC was performed using Merck silica gel F_{254} (10-12 μm) plates and analyzed by UV light or by staining upon heating either with ninhydrin solution (1 g ninhydrin, 100 mL ethanol, 5 drops glacial acetic acid), PMA solution (2.5 g fosfomolybdic acid, 100 mL EtOH, 5 mL conc. H_2SO_4, 1.5 mL 85% H_3PO_4) or $KMnO_4$ solution (1 g $KMnO_4$, 2 g Na_2CO_3, 100 mL H_2O). For silica gel chromatography, the flash chromatography technique was used, with Merck silica gel 60 (40-63 μm) and p.a. grade solvents unless otherwise noted.

IR spectra were recorded on a Perkin-Elmer Spectrum One spectrometer. Optical rotations were obtained with a Perkin-Elmer 343 polarimeter. The ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or in *d4*-MeOD on a Bruker Avance 400 (^1H 399.98 MHz; ^{13}C 100.59 MHz) spectrometer. The chemical shifts are reported in

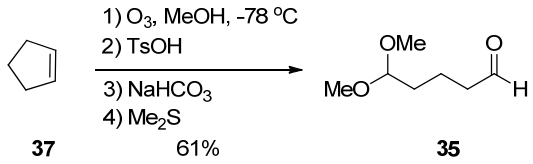
ppm relative to residual $CHCl_3$ (δ 7.26) or residual MeOH (δ 3.31) for ^1H NMR. For the ^{13}C NMR spectra, the residual $CDCl_3$ (δ 77.0) and *d4*-MeOD (δ 49.0) were used as the internal standard. HRMS-spectra were recorded on Waters LCT Premier –spectrometer. The enantiomeric excess (ee) of the IMDA products were determined by GC in comparison to the corresponding racemic samples using a Hewlett Packard HP 5890 instrument, Supelco β-Dex™ 120 column (30 m x 0.25 mm, 0.25 μm film) in isotherm (130 °C), helium as carrier gas (34 cm/s), with Hewlett Packard 5971 MS detector (270 °C) for ee analysis and isotherm (145 °C), helium as carrier gas (33 cm/s) for de analysis.

Oxidation experiments were carried in non-dry acetonitrile (Rathburn HPLC grade grade, water content unknown) and monitored using Shimadzu GC2010 gas chromatograph with FID detector equipped with Zebron ZB-35 column.

7.2 Synthesis of amaminol A

7.2.1 Early steps of the synthesis

*7.2.1.1 5,5-Dimethoxypentanal (**35**)*

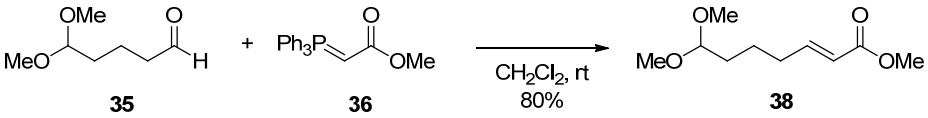


37 61% **35**

Following a literature procedure.[18] Cyclopentene (13.6 g, 200 mmol, 100 mol %) was dissolved in dry methanol (700 mL) and cooled to -78 °C. Ozone was bubbled through reaction mixture approximately 60 min until solution was light blue coloured (excess of O_3). Reaction mixture was bubbled with oxygen for 10 min and then atmosphere was replaced with argon. *p*-Toluene sulphonic adic monohydrate (4.45 g, 11.7 mmol, 11 mol %) was added into reaction mixture and it was stirred for 1.5 h allowing to warm gradually towards room temperature. After specified time sodium bicarbonate (3.44 g, 20.5 mmol, 20 mol %) was added. After stirring for 30 min dimethylsulfide (32.1 mL, 440 mmol, 220 mol %) was added and reaction was stirred overnight. Volume of the reaction mixture was reduced to approximately 70 mL and residue was partitioned

between dichloromethane (200 mL) and distilled water (100 mL). Aqueous phase was extracted with dichloromethane (100 mL and 50 mL). Combined organic extracts were washed with brine (150 mL) and dried with anhydrous Na_2SO_4. Evaporation of the solvent and reduced pressure distillation afforded aldehyde **35** as clear liquid in 20.53 g yield (70%, from which 87% was product and the rest were impurities according to GC). Calculated total yield taking impurities into account was 61%. R_f = 0.41 (50% EtOAc / hexanes); ^{1}H-NMR (400 MHz, MeOD) δ 9.68 (t, *J* = 1.4 Hz, 1H), 4.36 (t, *J* = 5.3 Hz, 1H), 3.30 (s, 6H), 2.47 (dt, *J* = 1.4 Hz, 6.9 Hz, 2H), 1.50-1.70 (m, 4H). These data match those reported in the literature.[174]

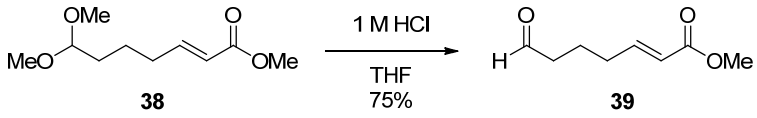
*7.2.1.2 (E)-Methyl-7,7-dimethoxy-hept-2-enoate (**38**)*



35 **36** **38**

Aldehyde **35** (9.7 g, 49.6 mmol, 100 mol %, purity ~74%) was dissolved in dry dichloromethane (250 mL) at room temperature and methyl (triphenylphosphoran-ylidene)acetate **36** was added. Reaction was stirred overnight and then solvent was removed by evaporation. Residual white solids containing oil was diluted with hexane (100 mL). Solids were filtered off and washed with hexane (3 x 40 mL). Solvents were evaporated and residue was purified by reduced pressure distillation (1.1 mbar) giving ester **38** at 104-107 °C (oil bath 150 °C) as clear liquid in 8.02 g (80%, *E/Z*, 15:1) yield. R_f = 0.50 (50% EtOAc / hexanes); IR (thin film, cm^{-1}) 2950, 2831, 1725, 1658, 1436, 1272, 1195, 1128, 1069, 1049, 982; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.90 (dt, *J* = 6.9 Hz, 15.7 Hz, 1H), 5.78 (dt, *J* = 1.6 Hz, 15.6 Hz, 1H), 4.31 (t, *J* = 5.5 Hz, 1H), 3.67 (s, 3H), 3.26 (s, 6H), 2.14-2.22 (m, 2H), 1.53-1.61 (m, 2H), 1.43-1.53 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.8, 148.8, 121.1, 104.1, 52.6, 51.2, 31.8, 31.7, 22.9; HRMS (ESI) calc. for [M+Na] $C_{10}H_{18}O_4Na$ 225.1103, found 225.1112, Δ = 4.0 ppm.

*7.2.1.3 (E)-Methyl-7-oxo-hept-2-enoate (**39**)*

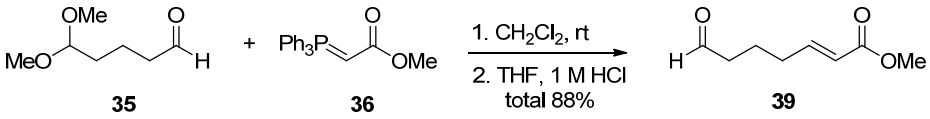


38 **39**

Acetal **38** (7.968 g, 39.4 mmol, 100 mol %) was dissolved in THF (100 mL) and aqueous 1 M HCl –solution (100 mL). Reaction was strirred for 30 min and ether (100 mL) was added. Aqueous phase was extracted with ether (3 x 50 mL). Combined organic extracts were washed with brine (100 mL), dried with anhydrous Na_2SO_4 and evaporated to dryness. Crude product was purified by reduced pressure (0.2 mbar) distillation at 70-71 °C (oil bath 120 °C) to afford aldehyde **39** as clear liquid in 4.65 g (75%) yield. R_f = 0.42 (50% EtOAc / hexanes); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.4 Hz, 1H), 6.92 (dt, *J* = 6.9 Hz, 15.6 Hz, 1H), 5.85 (dt, *J* = 1.5 Hz, 15.6 Hz, 1H), 3.73 (s, 3H), 2.49 (dt, *J* = 1.3 Hz, 7.2 Hz, 2H), 2.25 (ddt, *J* = 1.3 Hz, 7.2 Hz, 7.3 Hz, 2H), 1.81 (ddt, *J* = 7.3 Hz, 7.3 Hz, 7.3 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 201.5, 166.8, 147.8, 121.8, 51.4, 42.9, 31.2, 20.3. These data match those reported in the literature.[175]

Procedure with a single purification:

*7.2.1.4 (E)-Methyl-7-oxo-hept-2-enoate (**39**)*



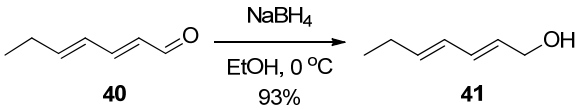
35 **36** **39**

Aldehyde **35** (20.5 g, 122.0 mmol, 100 mol %, purity ~87%) was dissolved in dry dichloromethane (280 mL) at room temperature and methyl (triphenylphosphoran-ylidene)acetate **36** was added. Reaction was stirred overnight and then solvent was removed by evaporation. Residual white solids containing oil was treated with hexane (100 mL). Solids were filtered off and washed with hexane (2 x 50 mL). Solvents were evaporated to give 29.76 g of crude acetal as clear oil.

This crude acetal was dissolved in THF (150 mL) and aqueous 1 M HCl –solution (150 mL). Reaction was strirred for 30 min and ether (150 mL) was added. Aqueous phase was extracted with ether (3 x 100 mL). Combined organic extracts were washed

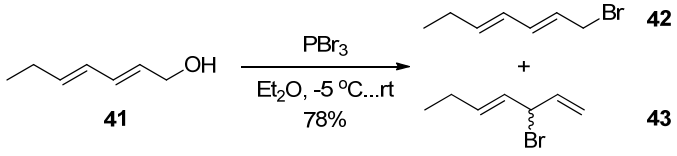
with brine (200 mL), dried with anhydrous sodium sulfate and evaporated to dryness. Crude product was purified by reduced pressure (0.2 mbar) distillation at 70-71 °C (oil bath 120 °C) to afford aldehyde **39** as clear liquid in 16.9 g (88% over two steps) yield. Geometrical isomer-ratio was found to be 20:1 (*E:Z*). For characterization data see synthesis procedure 7.2.1.3.

*7.2.1.5 (E,E)-Heptadienol (**41**)*



Heptadienal **40** (28.4 mL, 200 mmol, 100 mol %, Kosher grade >88%) was dissolved in EtOH (200 mL) and cooled to 0 °C. Sodium borohydride (7.6 g, 200 mmol, 100 mol %) was added and reaction was stirred for 60 min. Solvent was mainly evaporated and residue was partitioned between ether (200 mL) and aqueous 1 M NaOH solution (200 mL). Aqueous phase was extracted with ether (100 mL). Combined organic extracts were washed with brine (150 mL), dried with anhydrous Na_2SO_4 and evaporated to give 25.1 g of yellow oil. Product was purified by reduced pressure (11 mmHg) distillation giving alcohol **41** at 88-90 °C (oil bath 130 °C) as clear liquid in 20.9 g (93%) yield. R_f = 0.19 (20% EtOAc / hexanes); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.22 (dd, *J* = 10.1 Hz, 15.1 Hz, 1H), 6.04 (dd, *J* = 10.2 Hz, 15.0 Hz, 1H), 5.68-5.80 (m, 2H), 4.16 (t, *J* = 5.6 Hz, 2H), 2.10 (dq, *J* = 6.4 Hz, 7.1 Hz, 2H), 1.34 (t, *J* = 5.8 Hz, 1H), 1.01 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.2, 132.1, 129.3, 128.3, 63.5, 25.6, 13.4.[176]

*7.2.1.6 (2E,4E)-1-Bromohepta-2,4-diene (**42**) and (E)-3-bromohepta-1,4-diene (**43**)*



A slurry of (*2E,4E*)-hepta-2,4-dienol **41** (20.8 g, 186 mmol, 100 mol %) and calcium hydride (11.7 g, 279 mmol, 150 mol %) in dry ether (150 mL) was stirred for 60 minutes. Reaction mixture was cooled to 0 ºC and phosphorous tribromide (6.6 mL,

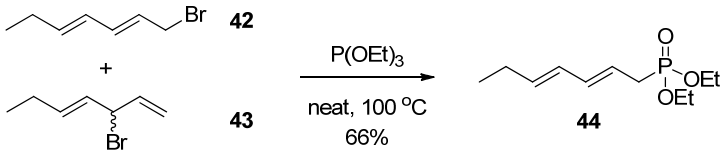
69.8 mmol, 37.5 mol %) in dry ether (20 mL) was added in multiple portions. After 60 minutes reaction was quenched by addition of methanol (0.89 mL, 27.9 mmol, 15 mol %) after which the reaction was allowed to warm to room temperature. Mixture was filtered trough celite followed by ether washings (2 x 50 mL). Solvent was evaporated and crude product was purified by reduced pressure distillation (4 mmHg, oil bath 80 ºC) to afford 23.4 g (72%) of a 2:1 mixture of bromides **42** and **43** as slightly yellow oil. Product decomposes at room temperature but it was found to be only slight decomposed when kept four months in a freezer (-18 ºC). R_f = 0.67 (20% EtOAc / hexanes).

For **42:** ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.16-6.37 (m, 1H), 6.03 (dd, J = 10.4 Hz, 15.2 Hz, 1H), 5.71-5.89 (m, 2H), 4.03 (d, J = 7.8 Hz, 2H), 2.12 (dq, J = 6.3 Hz, 7.0 Hz, 2H), 1.01 (t, J = 7.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 139.1, 135.3, 127.8, 126.1, 33.8, 25.6, 13.2.

For **43:** ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.26 (dd, J = 1.2 Hz, 16.5 Hz, 1H), 5.15 (dd, J = 1.2 Hz, 9.7 Hz, 1H), 4.51 (dt, J = 6.8 Hz, 9.4 Hz, 1H), 1.86-2.05 (m, 2H), 1.00 (t, J = 7.3 Hz). Other proton signals were obscured; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.6, 134.3, 132.4, 119.0, 57.5, 32.3, 12.3.

7.2.2 Horner-Wadsworth-Emmons reaction approach

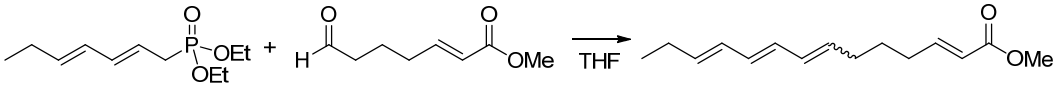
*7.2.2.1 ((2E,4E)-Hepta-2,4-dienyl)-phosphonic acid diethyl ester (**44**)*



A mixture of **42** and **43** (0.883 g, 5.0 mmol, 100 mol %) was dissolved in freshly distilled triethyl phosphite (5 mL) and heated to 100 °C. Reaction was stirred for 1 h and allowed to cool down. Excess of triethyl phosphite was distilled off under reduced pressure (18 mmHg, oil bath 90 °C). Residual yellow oil was distilled using Kugelrohr apparatus to give 0.079 g as fraction A (0.3 mmHg, air bath 80 °C) which was discarded and 0.773 g (66%) as fraction B (0.3 mmHg, air bath 110 °C) identified to be phophonate **44**. R_f = 0.18 (EtOAc); IR (thin film, cm^{-1}) 3468, 2966, 2933, 1457, 1443,

1392, 1252, 1028, 988, 962, 843, 720; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.08 (m, 1H), 6.02 (ddd, *J* = 1.2 Hz, 10.3 Hz, 15.4 Hz, 1H), 5.68 (ddt, *J* = 2.3 Hz, 6.5 Hz, 15.0 Hz, 1H), 5.5 (dq, *J* = 7.4 Hz, 14.9 Hz, 1H), 4.03-4.16 (m, 4H), 2.61 (dd, *J* = 7.5 Hz, 22.2 Hz, 2H), 2.03-2.14 (m, 2H), 1.31 (t, *J* = 7.0 Hz, 6H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ [136.2, 136.1], [135.3, 135.2], [128.54, 128.4], [119.2, 119.1], [61.9, 61.8], [31.2, 29.9], [25.5, 25.5], [16.4, 16.3], [13.3, 13.3]; HRMS (ESI) calc. for [M+Na] $C_{11}H_{21}NaO_3P$ 255.1126, found 255.1136, Δ = 3.9 ppm.

Table 9. HWE-reaction optimimizations.

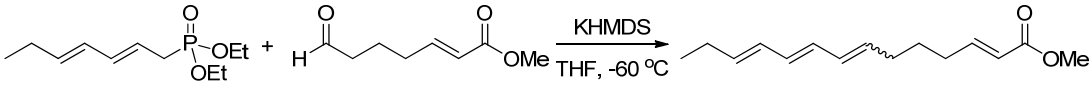


44 **39** **45**

Entry	**44** (equiv)	**39** (equiv)	Base	Temp. (°C)	Yield **45** (%)
1[a]	1.2	1	1.2 equiv KOt-Bu	-78…-50	2.8
2	1.2	1	1.2 equiv KOt-Bu	-78…rt	NI[b]
3	1.2	1	1.2 equiv BuLi	-78…rt	NI[b]
4	1.2	1	1.2 equiv KHMDS	-78…-40	8.5[c]
5	1.2	1	1.2 equiv LDA	-78…rt	NI[b]
6	1	3[d]	1.1 equiv KHMDS	-78…-40	NI[b]

General Procedure: Base was added onto solution of **44** and after 15-30 min aldehyde **39** in THF was added. a) Both **44** and **39** were added onto a slurry of base. b) NI = not isolated. All these reaction showed trace of products but crude ^{1}H NMR showed not to be worth to isolate. c) *E/Z* ratio >10:1. d) Even excess of aldehyde was consumed.

*7.2.2.2 (2E,7E,9E,11E)-Tetradeca-2,7,9,11-tetraenoic acid methyl ester **45***



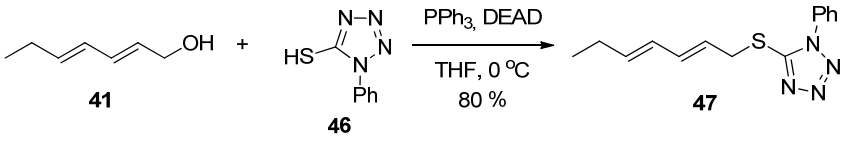
44 **39** **45**

Phosphonate **44** (0.083 g, 0.36 mmol, 120 mol %) was dissolved in dry THF (2 mL) and cooled to -60 °C. To this solution was added 0.5 M KHMDS in toluene (0.72 mL, 0.36 mmol, 120 mol %) which gave orange solution. After 10 min precooled solution of aldehyde **39** (0.046 g, 0.30 mmol, 100 mol %) in dry THF (1 mL) was added. Reaction was stirred for 1 h at which time temperature rose to -40 °C. Reaction was quenched by addition saturated aqueous NH_4Cl –solution (3 mL) and ether (3 mL). Mixture was allowed to warm to room temperature and aqueous phase was extracted with ether

(3 mL). Combined organic extracts were washed with brine, dried with anhydrous Na_2SO_4 and evaporated to dryness. Crude product was purified with silica gel chromatography using 5% EtOAc / hexanes to yield 0.006 g (8.5%) of tetraene **45** as clear oil. Selectivity for C7-double bond was found to be >10:1 (*E/Z*). R_f = 0.48 (20% EtOAc / hexanes); IR (thin film, cm^{-1}) 3014, 2932, 2872, 1725, 1658, 1435, 1314, 1270, 1199, 1174, 1041, 993. For major isomer **8**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.95 (dt, *J* = 6.9 Hz, 15.6 Hz, 1H), 5.91-6.22 (m, 3H), 5.82 (dt, *J* = 1.5 Hz, 15.6 Hz, 1H), 5.71 (dt, *J* = 6.6 Hz, 14.3 Hz, 1H), 5.60 (dt, *J* = 7.0 Hz, 14.0 Hz, 1H), 3.72 (s, 3H), 2.05-2.26 (m, 6H), 1.55 (dq, *J* = 7.4 Hz, 7.4 Hz, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.0, 149.1, 136.2, 132.8, 131.3, 131.2, 130.4, 129.3, 121.0, 51.3, 32.0, 31.5, 27.5, 25.7, 13.5; HRMS (ESI) calc. for [M+Na] $C_{15}H_{22}O_2Na$ 257.1517, found 257.1504, Δ = 5.1 ppm.

7.2.3 Julia-Kocienski olefination approach

7.2.3.1 5-[(2E,4E)-Hepta-2,4-dienyl)sulfanyl]-1-phenyl-1H-tetrazole (47)

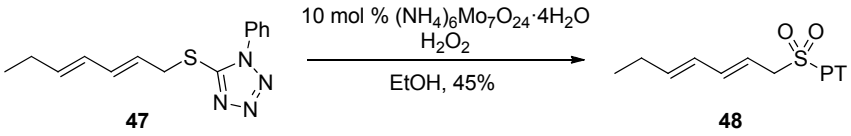


41 46 47

To a stirred solution of heptadienol **41** (0.038 mL, 0.30 mmol, 100 mol %), triphenylphosphine (0.089 g, 0.33 mmol, 110 mol %) and 1-phenyl-1*H*-tetrazole-5-thiol **46** (0.060 g, 0.33 mmol, 110 mol %) in dry THF (3 mL) was added diethyl azodicarboxylate (0.055 mL, 0.33 mmol, 110 mol %) at 0 °C. Reaction was stirred 2 h and the reaction mixture was allowed to warm to room temperature. Ether (5 mL) and saturated aqueous $NaHCO_3$ –solution (5 mL) were added. Aqueous phase was extracted with ether. Combined organic fractions were dried with anhydrous Na_2SO_4 and evaporated to dryness giving white solids containing oil. Crude product was purified using flash chromatography 5-10% EtOAc / hexanes as eluent to afford **47** (0.066 g, 80%) as clear oil. R_f = 0.34 (20% EtOAc / hexanes); IR (thin film, cm^{-1}) 3325, 3021, 2964, 2932, 2873, 1654, 1596, 1499, 1461, 1411, 1385, 1240, 1088, 1014, 988, 760, 693; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.48-7.60 (m, 5H), 6.31 (dd, *J* = 10.4 Hz, 15.0 Hz, 1H), 5.97 (dd, *J* = 10.4 Hz, 15.1 Hz, 1H), 5.63-5.82 (m, 2H), 4.05 (d, *J* = 7.5 Hz, 2H),

2.08 (dq, *J* = 7.3 Hz, 7.5 Hz, 2H), 0.99 (t, *J* = 7.5 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.8, 138.3, 135.8, 133.6, 130.0, 129.6, 127.8, 123.7, 122.9, 35.7, 25.5, 13.2; HRMS (ESI) calc. for [M+Na] $C_{14}H_{16}N_4NaS$ 295.0993, found 295.0995, Δ = 0.7 ppm.

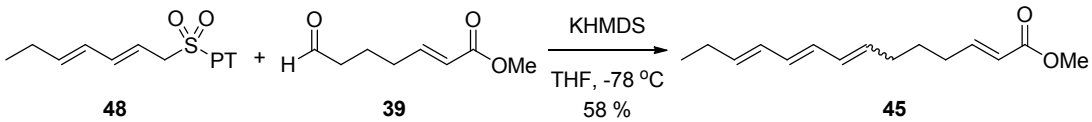
*7.2.3.2 5-[((2E,4E)-Hepta-2,4-diene)-1-sulfonyl]-1-phenyl-1H-tetrazole (**48**)*



47 **48**

To a stirred solution of sulfide **47** (0.064 g, 0.23 mmol, 100 mol %) in EtOH (1.5 mL) at 0 °C was added yellow solution of $(NH_4)_6Mo_7O_{24}\bullet H_2O$ (0.029 g, 0.02 mmol, 10 mol %) in 30 w % hydrogen peroxide (0.23 mL, 2.3 mmol, 1000 mol %). Reaction was allowed to warm to room temperature end stirred overnight. Solvents were mainly evaporated and residue was partitioned between dichloromethane (5 mL) and brine (5 mL). Aqueous phase was extracted with dichloromethane (3 mL). Combined organic fractions were washed with brine, dried with anhydrous Na_2SO_4 and evaporated to dryness. Crude product was purified using flash chromatography 5-10% EtOAc / hexanes as eluent affording 0.032 g (45%) of sulfone **48** as oil. R_f = 0.31 (20% EtOAc / hexanes); IR (thin film, cm^{-1}) 2965, 2931, 1653, 1595, 1497, 1343, 1152, 992, 763, 688, 631; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54-7.66 (m, 5H), 6.36 (dd, *J* = 10.3 Hz, 15.1 Hz, 1H), 6.01 (dd, *J* = 10.2 Hz, 15.3 Hz, 1H), 5.86 (dt, *J* = 6.4 Hz, 15.2 Hz, 1H), 5.49 (dt, *J* = 7.6 Hz, 15.3 Hz, 1H), 4.41 (d, *J* = 7.5 Hz, 2H), 2.11 (dq, *J* = 7.4 Hz, 7.5 Hz, 2H), 1.00 (t, J = 7.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.1, 142.4, 141.2, 132.9, 131.4, 129.5, 127.4, 125.2, 111.9, 60.0, 25.6, 13.0; HRMS (ESI) calc. for [M+Na] $C_{14}H_{16}N_4NaO_2S$ 327.0892, found 327.0884, Δ = 2.4 ppm.

*7.2.3.3 (2E,7E,9E,11E)-Tetradeca-2,7,9,11-tetraenoic acid methyl ester (**45**)*



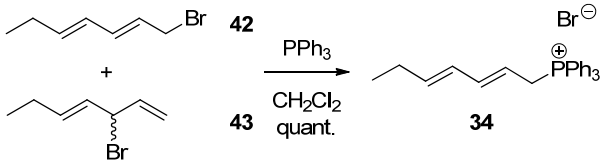
48 **39** **45**

To a stirred solution of sulfone **48** (0.032 g, 0.10 mmol, 120 mol %) in dry THF (1.5 mL) was added 0.5 M KHMDS in toluene (0.20 mL, 0.10 mmol, 120 mol %) at

-70 °C. After 10 min precooled solution of aldehyde **39** (0.013 g, 0.08 mmol, 100 mol %) in dry THF (0.5 mL) to this bright orange reaction mixture. Reaction was stirred 3 h maintaining temperature at -50…-70 °C. Reaction was quenched by addition of saturated aqueous NH_4Cl –solution. Mixture was diluted with ether and aqueous phase was extracted with ether. Combined organic extracts were dried with anhydrous Na_2SO_4 and evaporated to dryness. Product was purified with flash chromatography using 5% EtOAc / hexanes yielding tetraene **45** (0.012 g, 58%) as oil. Selectivity for C7-double bond was found to be 4:6 (*E/Z*). For characterization data see synthesis procedure 7.2.2.2.

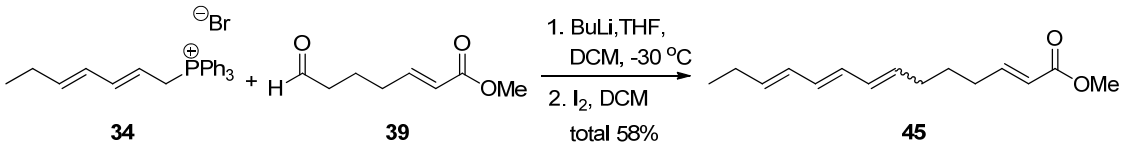
7.2.4 Wittig olefination approach

*7.2.4.1 (2E,4E)-Hepta-2,4-dienyltriphenylphosphonium bromide (**34**)*



Literature example of this procedure.[17] Triphenyl phosphine (32.2 g, 123 mmol, 100 mol %) was dissolved in dry dichloromethane (250 mL) and mixture of bromides **42** and **43** (22.6 g, 129 mmol, 105 mol %) was added at 0 °C. Reaction was allowed to wrm to room temperature and stirred for 15 hours. Solvent was evaporated to give 54.7 g (quant.) of phosphonium salt **34** as white foam after kept 24 hours under high vacuo. Product is highly hygroscopic, light sensitive and decomposes at room temperature and therefore it was used as such. It was found to be stable in a freezer (-18 °C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.64-7.89 (m, 15H), 6.37 (ddd, *J* = 5.1 Hz, 10.2 Hz, 15.1 Hz, 1H), 5.89 (dd, *J* = 10.8 Hz, 14.7 Hz, 1H), 5.69 (ddt, *J* = 2.4 Hz, 4.8 Hz, 11.9 Hz, 1H), 5.27-5.38 (m, 1H), 4.75 (dd, *J* = 7.4 Hz, 15.2 Hz, 2H), 2.03 (dq, *J* = 7.5 Hz, 7.7 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ [140.9, 140.7], [139.5, 139.4], [134.9, 134.9], [133.9, 133.8], [130.2, 130.1], [127.5, 127.4], [118.4, 117.6], [113.3, 113.1], [28.4, 28.9], [25.8, 25.4], [13.0, 13.0].

*7.2.4.2 (2E,7E,9E,11E)-Methyl tetradeca-2,7,9,11-tetraenoate (**45**)*

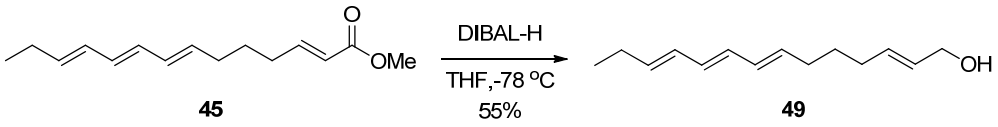


34 **39** **45**

Phosphonium salt **34** (4.42 g, 9.6 mmol, 120 mol %, purity estimated to be ~95%) was dissolved in dry THF (50 mL) and dry dichloromethane (15 mL). Yellow solution was cooled to -30 °C and 2.12 M butyl lithium in hexanes (4.5 mL, 9.6 mmol, 120 mol %) was added resulting a red mixture. Reaction was stirred for 60 minutes and aldehyde **39** (1.25 g, 8.0 mmol, 100 mol %) in dry THF (25 mL) was added. Reaction was stirred another 60 minutes and then allowed to warm to room temperature. After 30 minutes reaction was quenched by addition of saturated ammonium chloride solution (80 mL). Dichloromethane (80 mL) was added and phases were separated. Aqueous phase was extracted with dichloromethane (50 mL). Combined organic extracts were washed with brine (100 mL), dried with anhydrous sodium sulfate and evaporated to dryness. Crude product was filtered trough 3 cm pad of silica using dichloromethane. Solvents were evaporated and product was purified by flash chromatography using 3% ethyl acetate in hexanes to afford 1.11 g (59%) of ester **45** as yellow oil. NMR showed *7E:7Z* ratio to be 1.2:1.

Product (4.73 mmol) was dissolved in dichloromethane (25 mL) and iodine (60 mg, 0.23 mmol, 5 mol %) was added. Mixture was stirred for 15 minutes and saturated solution of sodium thiosulfate (25 mL) was added. Biphasic mixture was stirred vigorously for 30 minutes. Phases were separated and aqueous phase was extracted with dichloromethane (25 mL). Combined organic extracts were washed with brine (30 mL), dried with anhydrous sodium sulfate and evaporated to dryness to give 1.09 g (total 58% over two steps) of ester **45** in 4:1 (*7E:7Z*) ratio as yellow oil. For characterization data see synthesis procedure 7.2.2.2.

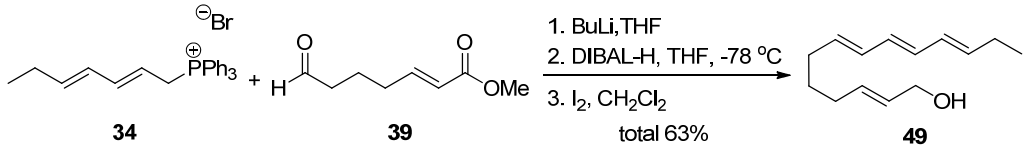
*7.2.4.3 (2E,7E,9E,11E)-Tetradeca-2,7,9,11-tetraen-1-ol (**49**)*



45 **49**

Ester **45** (1.09 g, 4.65 mmol, 100 mol %) was dissolved in dry THF (25 mL) and cooled to -78 ºC. To this solution was added 1.0 M diisobutyl aluminium hydride in toluene (13.9 mL, 13.9 mmol, 300 mol %) and reaction was stirred for 60 minutes. Reaction was quenched by addition of methanol (5.5 mL) and mixture was allowed to warm to room temperature. After 80 minutes 0.5 M phosphoric acid (50 mL) and dichloromethane (50 mL) were added. Mixture was stirred vigorously for 60 minutes and phases were separated. Aqueous phase was extracted with dichloromethane (30 mL). Combined organic extracts were dried with anhydrous sodium sulfate and evaporated to dryness. Crude product was purified by flash chromatography using 30% ethyl acetate in hexanes to give 0.53 g (55%) of alcohol **49** as clear oil. R_f = 0.20 (20% EtOAc / hexanes); IR (thin film, cm^{-1}) 3338, 3012, 2962, 2929, 2855, 1455, 1437, 1088, 993, 968. For major isomer **49**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.92-6.22 (m, 4H), 5.57-5.79 (m, 4H), 4.08 (br s, 2H), 2.01-2.26 (m, 6H), 1.48 [dq, J = 7.5 Hz, (d), 2H], 1.28 (br s, 1H), 1.00 (t, J = 7.54 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 136.0, 133.6, 132.8, 131.0, 130.8, 130.6, 129.4, 129.2, 32.1, 31.5, 28.6, 25.7, 13.5; HRMS (ESI) calc. for [M+Na] $C_{14}H_{22}ONa$ 229.1568, found 229.1517, Δ = 1.3 ppm.

*7.2.4.4 (2E,7E,9E,11E)-Tetradeca-2,7,9,11-tetraen-1-ol (**49**)*



34 **39** total 63% **49**

Phosphonium salt **34** (29.7 g, 64.6 mmol, 120 mol %, purity estimated to be ~95%) in THF (200 mL) was cooled to -30 °C. To this slurry was added 1.80 M butyl lithium (35.9 mL, 64.6 mmol, 120 mol %) in hexanes during 20 minutes resulting a red slurry. Mixture was stirred for 10 minutes and aldehyde **39** (8.4 g, 53.8 mmol, 100 mol %) in dry THF (30 mL) was cannulated into reaction mixture. Reaction was allowed to warm to room temperature and stirring was continued for 1 h. Reaction was quenched by

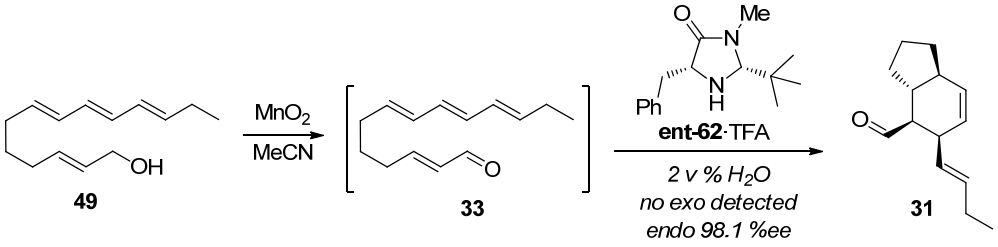
pouring the reaction mixture onto aqueous saturated NH_4Cl -solution (250 mL). Also ether (250 mL) was added and phases were separated. Aqueous phase was extracted with ether (150 mL). Combined organic extracts were washed with brine (400 mL), dried with anhydrous sodium sulfate. Solvents were evaporated and residual solids containing oil was treated with hexanes (100 mL) and ether (100 mL). Solids were filtered off and rinsed with ether (3 x 50 mL). Evaporation of solvents gave 15.4 g of crude ester as yellow oil. Geometrical isomer ratio was found to be 2:1 (*E:Z*).

Crude ester was dissolved in dry THF (130 mL) and cooled to -78 ºC. To this solution was added 1.0 M diisobutyl aluminium hydride in toluene (161 mL, 161 mmol, 300 mol %) and reaction was stirred for 1 h. Reaction was quenched by addition of aqueous saturated solution of Rochelle's salt (200 mL) and mixture was allowed to warm to room temperature. After 18 h phases were separated and aqueous phase was extracted with ether (200 mL). Combined organic extracts were washed with brine (300 mL), dried with anhydrous sodium sulfate and evaporated to dryness. Crude product was dissolved in dichloromethane (50 mL) and adsorbed on silica (3 x crude mass). Product was extracted by silica filtration using 10-30% ethyl acetate in hexanes to give 9.67 g (87%) of alcohol **49** as clear oil.

Alcohol **49** was dissolved in dichloromethane (94 mL) and treated with iodine (0.59 g, 2.34 mmol, 5 mol %). Mixture was stirred for 30 minutes and saturated solution of sodium thiosulfate (95 mL) was added. Biphasic mixture was stirred vigorously for 30 minutes. Phases were separated and aqueous phase was extracted with dichloromethane (100 mL). Combined organic extracts were washed with brine (100 mL), dried with anhydrous sodium sulfate and evaporated to dryness to give 8.06 g of alcohol **49**. This material required a second purification with silica gel chromatography affording 6.99 g (total yield of 63% over three steps) of alcohol **49** as clear oil. Geometrical isomer ratio was 4:1 (*E:Z*). For characterization data see synthesis procedure 7.2.4.3.

7.2.5 Construction of C1-C18 carbon skeleton of amaminol A

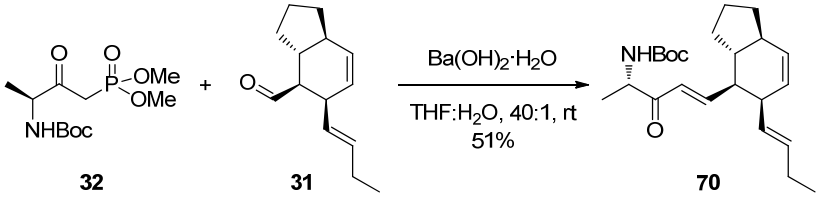
*7.2.5.1 (3aR,4S,5R,7aS)-5-[(E)-But-1-enyl]-2,3,3a,4,5,7a-hexahydro-1H-indene-4-carbaldehyde (**31**).*



Alcohol **49** (1.03 g, 5.0 mmol, 100 mol %) was dissolved in acetonitrile (40 mL) and manganese oxide (4.35 g, 50.0 mmol, 1000 mol %) was added. Reaction was stirred for 1 hour at room temperature. Second portion of manganese oxide (3.44 g, 39.5 mmol, 790 mol %) was added. After 5 hours, mixture was filtered trough celite followed by MeCN rinsing (2 x 10 mL). Resulting aldehyde **33** containing yellow solution was cooled to -20 ºC and distilled water (1 mL) was added. Catalyst **ent-62** (0.25 g, 1.0 mmol, 20 mol %) and trifluoroacetic acid (77 µL, 1.0 mmol, 20 mol %) were added and reaction was stirred at -18 ºC for 18 hours. Reaction was quenched by addition of 1% aqueous solution of $NaHCO_3$ (100 mL). Also pentane (60 mL) was added and mixture was allowed to warm to room temperature. Aqueous phase was extracted with pentane (2 x 50 mL). Combined organic extracts were washed with brine (100 mL), dried with anhydrous sodium sulfate and evaporated carefully (> 300 mmHg, water bath 25 ºC) to dryness to give 0.90 g of yellow oil. Crude product was purified by flash chromatography using 5% ether in pentane to afford 0.36 g (35% over two steps) of aldehyde **31** as clear oil. GC-MS analysis showed >308:1 *endo:exo* (no *exo* detected) and 98.1% ee selectivities. Product is highly volatile. R_f = 0.54 (20% EtOAc / hexanes); IR (thin film, cm^{-1}) 3018, 2959, 2871, 1723, 1455, 1066, 968; $[\alpha]^{20}$ = -223.8° (c 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.64 (d, *J* = 2.9 Hz, 1H), 5.90 (d, *J* = 9.8 Hz, 1H), 5.55 (dt, *J* = 6.3 Hz, 15.1 Hz, 1H), 5.43 (ddd, *J* = 2.6 Hz, 4.1 Hz, 9.7 Hz, 1H), 5.33 (ddt, *J* = 1.4 Hz, 8.7 Hz, 15.2 Hz, 1H), 3.28-3.38 (m, 1H), 2.53 (ddd, *J* = 2.9 Hz, 6.3 Hz, 11.4 Hz, 1H), 1.95-2.04 (m, 3H), 1.61-1.92 (m, 5H), 1.06-1.24 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 204.8, 135.3, 129.7, 129.3, 127.6, 56.1, 44.9,

41.1, 39.5, 28.4, 27.5, 25.4, 22.3, 13.6; HRMS (ESI) calc. for [M+Na] $C_{14}H_{20}ONa$ 227.1412, found 227.1410, Δ = 0.9 ppm.

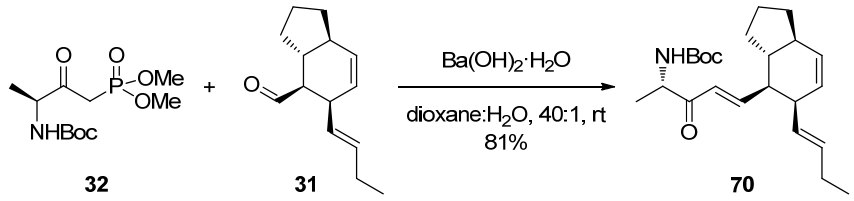
*7.2.5.2 tert-Butyl (S,E)-5-{(3aR,4S,5R,7aS)-5-[(E)-but-1-enyl]-2,3,3a,4,5,7a-hexahydro-1H-inden-4-yl}-3-oxopent-4-en-2-ylcarbamate (**70**)*



32 **31** **70**

Activated (kept 1 hour under high vacuo at 130-140 ºC) barium hydroxide (0.156 g, 0.91 mmol, 55 mol %) was mixed with phosphonate **32**[38] (0.537 g, 1.82 mmol, 110 mol %) in THF (10 mL) for 10 minutes. To this mixture was added aldehyde **31** (0.338 g, 1.65 mmol, 100 mol %) in 40:1 THF:H_2O (10 mL) and reaction was stirred at room temperature 24 hours. Reaction mixture was diluted with ether (20 mL) and 0.5 M phosphoric acid (20 mL) was added. Mixture was stirred vigorously until clear. Phases were separated and aqueous phase was extracted with ether (20 mL). Combined organic extracts were washed with brine (50 mL), dried with anhydrous sodium sulfate and evaporated to dryness. Crude product was purified by flash chromatography using 20% ether in hexanes to give 0.317 g (51%) of enone **70** as clear oil. R_f = 0.47 (20% EtOAc / hexanes); IR (thin film, cm^{-1}) 3426, 2962, 2871, 1716, 1695, 1627, 1492, 1446, 1366, 1167, 1044, 1019; $[\alpha]^{20}$ = -151.6° (c 1.0, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.87 (dd, *J* = 9.9 Hz, 15.8 Hz, 1H), 6.09 (d, *J* = 15.9 Hz, 1H), 5.88 (d, *J* = 9.7 Hz, 1H), 5.21-5.53 (m, 4H), 4.65 (dq, *J* = 9.9 Hz, 15.8 Hz, 1H), 2.49 [ddd, *J* = 6.5 Hz, 10.5 Hz (d), 1H], 1.96-2.06 (m, 2H), 1.79-1.92 (m, 2H), 1.47-1.77 (m, 3H), 1.44 (s, 9H), 1.32 (d, *J* = 7.1 Hz, 3H), 1.12-1.30 (m, 1H), 0.99-1.10 (m, 1H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.5, 155.0, 152.4, 134.9, 129.9, 129.5, 128.1, 126.4, 79.4, 52.5, 48.1, 45.2, 45.1, 42.8, 28.9, 28.3, 27.9, 25.5, 22.0, 19.5, 13.7; HRMS (ESI) calc. for [M+Na] $C_{23}H_{35}NO_3Na$ 396.2515, found 396.2516, Δ = 0.3 ppm.

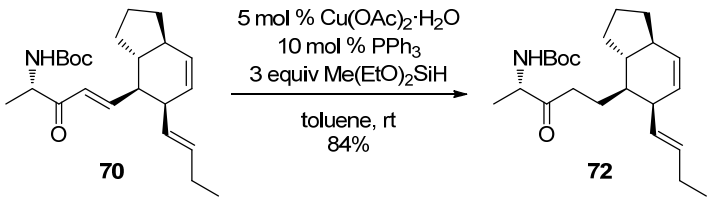
*7.2.5.3 tert-Butyl (S,E)-5-{(3aR,4S,5R,7aS)-5-[(E)-but-1-enyl]-2,3,3a,4,5,7a-hexahydro-1H-inden-4-yl}-3-oxopent-4-en-2-ylcarbamate (**70**)*



Activated (kept 1 hour under high vacuo at 130-140 ºC) barium hydroxide (0.143 g, 0.84 mmol, 55 mol %) was mixed with phosphonate **32**[38] (0.496 g, 1.68 mmol, 110 mol %) in 1,4-dioxane (15 mL) for 10 minutes. To this mixture was added aldehyde **31** (0.312 g, 1.52 mmol, 100 mol %) in dioxane (7 mL) and H_2O (0.44 mL). Reaction was stirred at room temperature 18 hours. Solvent was mainly evaporated. The residual mixture was diluted with ether (20 mL) and 0.5 M phosphoric acid (20 mL) was added. Phases were separated and aqueous phase was extracted with ether (10 mL). Combined organic extracts were washed with brine (20 mL), dried with anhydrous sodium sulfate and evaporated to dryness. Crude product was purified by flash chromatography using 10% ethyl acetate in hexanes to give 0.464 g (81%) of enone **70** as clear oil. For characterization data see synthesis procedure 7.2.5.2.

7.2.6 Selective reductions

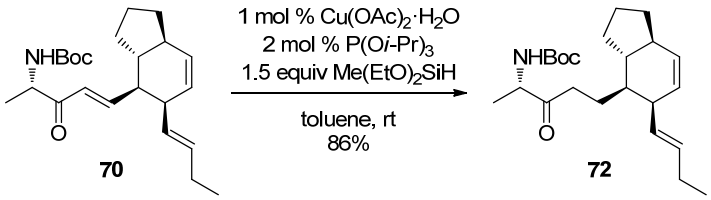
*7.2.6.1 tert-Butyl (S)-5-{(3aR,4S,5R,7aS)-5-[(E)-but-1-enyl]-2,3,3a,4,5,7a-hexahydro-1H-inden-4-yl}-3-oxopentan-2-ylcarbamate (**72**)*



A flask was charged with $Cu(OAc)_2 \bullet H_2O$ (0.015 g, 0.08 mmol, 5 mol %), triphenylphosphine (0.040 g, 0.15 mmol, 10 mol %), dry toluene (10 mL) and $Me(EtO)_2SiH$ (0.76 mL, 4.56 mmol, 300 mol %) under argon. Mixture was stirred for one hour while the color of the reaction mixture turned from blue to green and gradually brownish. Enone **70** (0.57 g, 1.52 mmol, 100 mol %) dissolved in dry toluene (5 mL)

was added and reaction was stirred for 2 h. Reaction was quenched with addition of acetic acid (0.46 mL, 7.60 mmol, 500 mol %) and 1 M TBAF solution in THF (2.3 mL, 2.3 mmol, 150 mol %). After 20 minutes solvents were evaporated. Crude product was purified by flash chromatography using 5-10% ethyl acetate in hexanes to afford 0.483 g (84%) of ketone **72** as clear oil. R_f = 0.42 (20 % EtOAc / hexanes); IR (thin film, cm^{-1}) 3359, 2958, 2928, 2869, 1711, 1494, 1454, 1366, 1247, 1170; $[\alpha]^{20}$ = -137.6° (c 0.9, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.80 (d, *J* = 9.6 Hz, 1H), 5.47 (dt, *J* = 6.3 Hz, 15.1 Hz, 1H), 5.38 (ddd, *J* = 2.6 Hz, 4.3 Hz, 9.7 Hz, 1H), 5.20-5.32 (m, 2H), 4.23-4.36 (m, 1H), 2.78-2.87 (m, 1H), 2.57 (ddd, *J* = 5.1 Hz, 10.7 Hz, 16.3 Hz, 1H), 2.39 (ddd, *J* = 6.0 Hz, 9.7 Hz, 15.9 Hz, 1H), 2.00 (ddq, *J* = 1.4 Hz, 7.5 Hz, 13.7 Hz, 2H), 1.61-1.86 (m, 5H), 1.45-1.60 (m, 2H), 1.42 (s, 9H), 1.20-1.33 (obs m, 2H), 1.30 (obs d, *J* = 7.1 Hz, 3H), 1.07-1.20 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 209.8, 155.1, 133.8, 130.7, 129.4, 128.3, 79.5, 54.7, 46.1, 44.6, 43.2, 42.0, 36.5, 29.2, 28.3, 27.8, 25.6, 25.0, 22.1, 18.1, 13.9; HRMS (ESI) calc. for [M+Na] $C_{23}H_{37}NO_3Na$ 398.2671, found 398.2672, Δ = 0.3 ppm.

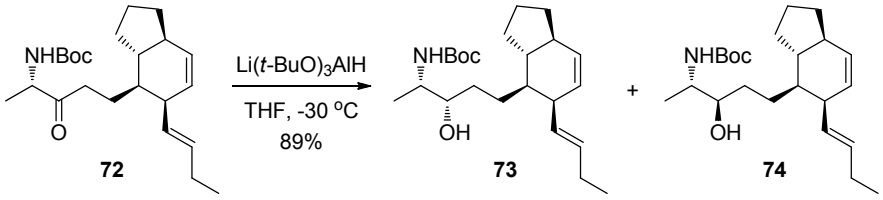
*7.2.6.2 tert-Butyl (S)-5-{(3aR,4S,5R,7aS)-5-[(E)-but-1-enyl]-2,3,3a,4,5,7a-hexahydro-1H-inden-4-yl}-3-oxopentan-2-ylcarbamate (**72**)*



A flask was charged with $Cu(OAc)_2$•H_2O (5 mg, 22 μmol, 1 mol %), tri-*iso*-propylphosphite (10 μL, 44 μmol, 2 mol %), dry toluene (5 mL) and $Me(EtO)_2SiH$ (0.54 mL, 3.35 mmol, 150 mol %) under argon. Mixture was stirred for 4 hours while the color of the reaction mixture turned from blue to green and gradually orange. Enone **70** (0.83 g, 2.23 mmol, 100 mol %) dissolved in dry toluene (6 mL) was added and reaction was stirred for 3.5 h. Reaction was quenched with addition of acetic acid (0.64 mL, 11.2 mmol, 500 mol %) and 1 M TBAF solution in THF (3.4 mL, 3.4 mmol, 150 mol %). After 10 minutes solvents were evaporated. Crude product was purified by flash chromatography using 5-10% ethyl acetate in hexanes to afford 0.727 g (86%) of

ketone **72** as clear oil which solidified later. For characterization data see synthesis procedure 7.2.6.1.

*7.2.6.3 N-Boc amaminol A (**73**) and N-Boc (2S,3R)-epi-amaminol A (**74**)*

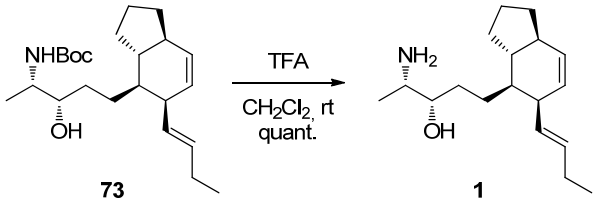


Ketone **72** (0.85 g, 2.27 mmol, 100 mol %) was dissolved in dry THF (23 mL). Solution was cooled to -30 °C and lithium tri-*tert*-butoxy aluminium hydride (1.74 g, 6.82 mmol, 300 mol %) was added. Reaction was stirred for 1.5 h. Mixture was diluted with ether (40 mL) and 0.5 M H_3PO_4 –solution (40 mL) was added. Mixture was allowed to warm to room temperature. Phases were separated and aqueous phase was extracted with ether (2 x 20 mL). Combined organic extracts were washed with brine (60 mL), dried with anhydrous sodium sulfate and evaporated to dryness. Crude product was purified by flash chromatography using 10-20% ethyl acetate in hexanes to give in eluation order fraction A 0.51 g (59%) of alcohol **73** as white crystalline solids and fraction B 0.26 g (30%) of a mixture of **73** and **74** as white solids. Total yield was 0.77 g (89%). Selectivity was found to be *syn :anti* 3:1 based on crude NMR data.

For **73:** R_f = 0.25 (20% EtOAc / hexanes); IR (thin film, cm^{-1}) 3436, 2959, 2869, 1687, 1504, 1454, 1366, 1247, 1170; $[\alpha]^{20}$ = -203.8° (c 1.0, $CHCl_3$ ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.80 (d, *J* = 9.6 Hz, 1H), 5.46 (dt, *J* = 6.3 Hz, 15.1 Hz, 1H), 5.39 (ddd, *J* = 2.5 Hz, 4.2 Hz, 9.5 Hz, 1H), 5.28 (dd, *J* = 9.0 Hz, 15.2 Hz, 1H), 4.65 (br s, 1H), 3.61 (br s, 1H), 3.38-3.49 (m, 1H), 2.79-2.91 (m, 1H), 2.01 [dq, *J* = 7.4 Hz (d), 2H], 1.62-1.92 (m, 6H), 1.50-1.62 (m, 2H), 1.20-1.49 (obs m, 4H), 1.44 (obs s, 9H), 1.07-1.20 (obs m, 2H), 1.15 (obs d, *J* = 6.7 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.1, 133.5, 131.0, 129.4, 128.6, 79.3, 75.1, 50.4, 46.2, 44.7, 43.1, 42.4, 31.1, 29.3, 28.3, 27.9, 26.3, 25.6, 22.1, 18.3, 13.9; HRMS (ESI) calc. for [M+Na] $C_{23}H_{39}NO_3Na$ 400.2828, found 400.2833, Δ = 1.2 ppm. These data match those obtained from the original spectra.[1,177]

For **74:** R_f = 0.20 (20% EtOAc / hexanes); IR (thin film, cm^{-1}) 3365, 2955, 2868, 1683, 1527, 1453, 1367, 1176, 1042; $[\alpha]^{20}$ = -217.9° (c 0.7, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.81 (d, *J* = 9.7 Hz, 1H), 5.46 (dt, *J* = 6.3 Hz, 15.1 Hz, 1H), 5.39 (ddd, *J* = 2.6 Hz, 4.4 Hz, 9.6 Hz, 1H), 5.26 (dd, *J* = 9.1 Hz, 15.1 Hz, 1H), 4.77 (br s, 1H), 3.67 (br s, 1H), 3.52-3.61 (m, 1H), 2.82-2.92 (m, 1H), 2.05-2.28 (m, 1H), 1.95-2.05 (m, 2H), 1.63-1.88 (m, 5H), 1.50-1.63 (m, 3H), 1.44 (s, 9H), 1.09-1.35 (m, 5H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.8, 133.4, 131.1, 129.3, 128.6, 79.4, 75.0, 50.3, 46.2, 44.7, 43.3, 43.1, 30.8, 29.3, 28.4, 27.9, 27.3, 25.6, 22.1, 14.3, 13.9; HRMS (ESI) calc. for [M+Na] $C_{23}H_{39}NO_3Na$ 400.2828, found 400.2824, Δ = 1.0 ppm.

*7.2.7 amaminol A (**1**)*



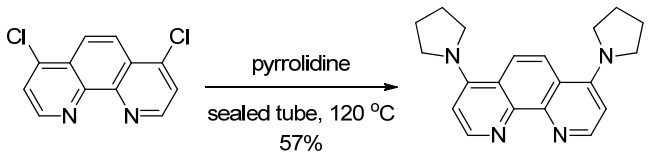
Alcohol **73** (0.068 g, 0.18 mmol, 100 mol %) was dissolved in dichloromethane (2 mL) and trifluoroacetic acid (0.2 mL) was added. After 2 hours reaction mixture was diluted with dichloromethane (4 mL) and 1 M NaOH –solution (4 mL) was added. Organic phase was washed with 1 M NaOH –solution (2 mL). Combined aqueous phases were extracted with dichloromethane (4 mL). Combined organic extracts were dried with anhydrous sodium sulfate and evaporated to give 0.051 g (quant.) of amaminol A **1** as oily solids. IR (thin film, cm^{-1}) 3262, 2958, 2870, 1739, 1601, 1454, 1077, 974; $[\alpha]^{20}$ = -214.8° (c 0.7, $CHCl_3$); ^{1}H-NMR (400 MHz, *d4*-MeOD) δ 5.79 (d, *J* = 9.87 Hz, 1H), 5.48 (dt, *J* = 5.9 Hz, 15.7 Hz, 1H), 5.29-5.43 (m, 2H), 3.16-3.27 (m, 1H), 2.84-2.93 (m, 1H), 2.69 (dq, *J* = 6.5 Hz (d), 1H), 2.03 [ddq, *J* = 1.1 Hz, 7.4 Hz (d), 2H], 1.66-1.88 (m, 5H), 1.56-1.66 (m, 1H), 1.34-1.55 (m, 4H), 1.10-1.25 (m, 2H), 1.04 (d, *J* = 6.4 Hz, 3H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (100 MHz, *d4*-MeOD) δ 134.7, 132.2, 130.1, 130.0, 77.2, 52.1, 47.7, 46.0, 44.2, 44.0, 31.7, 30.4, 28.9, 27.3, 26.7, 23.1, 19.3, 14.3; HRMS (ESI) calc. for [M+H] $C_{18}H_{32}NO$ 278.2484, found 278.2479, Δ = 1.8 ppm.

Amaminol A **1** was converted to its correspondind TFA salt for comparison with the original spectral data. For **1**•TFA: $[\alpha]^{20}$ = -88.3° (c 1.0, MeOH); ^{1}H-NMR (400 MHz, *d4*-MeOD) δ 5.80 (d, *J* = 9.7 Hz, 1H), 5.50 (dt, *J* = 6.2 Hz, 14.9 Hz, 1H), 5.29-5.43 (m, 2H), 3.46 (dt, *J* = 2.9 Hz, 7.6 Hz, 1H), 3.09 (dq, *J* = 6.6 Hz, 6.8 Hz, 1H), 2.85-2.94 (m, 1H), 1.98-2.08 (m, 2H), 1.67-1.89 (m, 5H), 1.36-1.66 (m, 5H), 1.25 (d, *J* = 6.7 Hz, 3H), 1.10-1.23 (m, 2H), 0.98 (t, *J* = 7.2 Hz); ^{13}C-NMR (100 MHz, *d4*-MeOD) δ 134.8, 132.0, 130.2, 129.9, 73.1, 53.1, 47.6, 45.9, 44.2, 44.0, 31.8, 30.4, 28.9, 26.8, 26.7, 23.1, 15.9, 14.3. These data match those reported in the literature.[1]

7.3 Aerobic oxidation experiments

7.3.1 Ligand synthesis

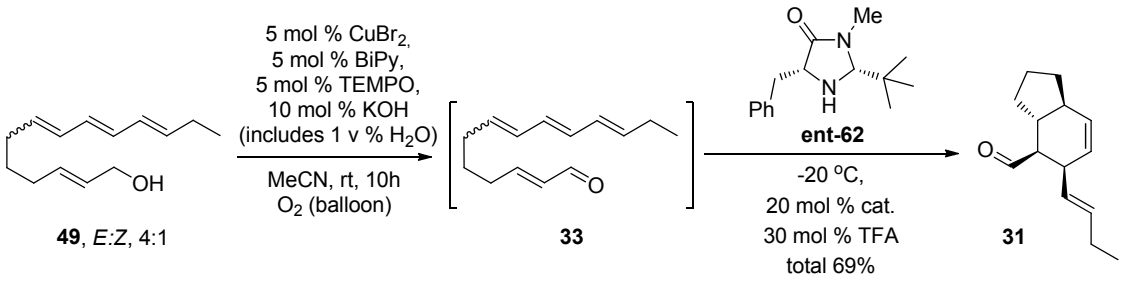
*7.3.1.1 4,7-di(pyrrolidin-1-yl)-1,10-phenanthroline (**339**)*



371 **339**

A 25 mL pressure flask was charged with 4,7-dichloro-1,10-phenanthroline[168] **371** (0.50 g, 2.0 mmol, 100 mol %) and pyrrolidine (10 mL). Container was sealed and heated to 120 °C with oil bath. Reaction mixture was stirred for 20 hours and then allowed to cool back to room temperature. Excess pyrrolidine was evaporated and residue was partitioned between aqueous 1 M NaOH –solution (10 mL) and dichloromethane (10 mL). Aqueous phase was extracted with dichloromethane (5 mL). Combined organic extracts were washed with brine (5 mL), dried with anhydrous sodium sulfate and evaporated to dryness to give 0.81 g of light brown solids. Crude product was recrystallized from ethanol (2mL) to give 0.36 g (57%) of **339** as natural white needles. mp. 188-192 °C (decomp.); IR (thin film, cm^{-1}) 2964, 2949, 2866, 1600, 1575, 1555, 1523, 1432, 1351, 1288, 805, 775; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.87 (d, *J* = 5.4 Hz, 2H), 7.93 (s, 2H), 6.70 (d, *J* = 5.4 Hz, 2H), 3.64-3.70 (m, 8H), 2.00-2.08 (m, 8H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 152.8, 149.2, 148.3, 119.4, 119.3, 105.5, 52.2, 25.9; HRMS (ESI) calc. for [M+H] $C_{20}H_{23}N_4$ 319.1923, found 319.1932, Δ = 2.8 ppm.

7.3.2 Aerobic oxidation in amaminol synthesis



Alcohol **49** (0.50 g, 2.42 mmol, 100 mol %) was dissolved in acetonitrile (24 mL). Copper(II) bromide (0.026 g, 0.12 mmol, 5 mol %) was added followed by BiPy (0.019 g, 0.12 mmol, 5 mol %) transforming colour to brown and back to green. After 6 minutes TEMPO (0.019 g, 0.12 mmol, 5 mol %) was added followed by aqueous 1 M KOH –solution (0.24 mL, 0.24 mmol, 10 mol %) turning colour to dark green and forming some solids into the reaction mixture. Reaction vessel was equipped with oxygen balloon and stirred at room temperature for 11 hours. Oxygen balloon was removed and reaction was cooled to -20 °C. Catalyst **ent-62** (0.119 g, 0.48 mmol, 20 mol %) was added followed by trifluoroacetic acid (0.098 mL, 0.73 mmol, 30 mol %). Reaction was stirred at -18 °C for 15 hours. Reaction was quenched by addition of aqueous 1% $NaHCO_3$ –solution (20 mL) and pentane (20 mL) and then allowed to warm to room temperature. Aqueous phase was extracted twice with pentane (20 mL, 10 mL). Combined organic extracts were washed with distilled water (20 mL), brine (20 mL) and dried with anhydrous sodium sulfate. Solvent was carefully evaporated (pressure >300 mmHg, bath 25 °C) to afford 0.677 g of clear oil. Crude product was purified with flash chromatography by using 5% ether / pentane to give 0.342 g (69%) of aldehyde **31** as clear oil. For characterization data see synthesis procedure 7.2.5.1.

7.3.3 Typical oxidation experiments

7.3.3.1 Typical oxidation experiment for catalyst component study (Figures 11-27).

Standard solution (0.5 M, 2 mL) of *trans*-2-hexen-1-ol **331** (1.0 mmol, 100 mol %) and internal standard *o*-xylene (1.0 mmol, 100 mol %) in acetonitrile was added into 25 mL round bottomed flask equipped with magnetic stir bar. To this was added copper(II)

bromide (0.02 mmol, 2 mol %) solution (20 mM, 1mL) in acetonitrile. To the ensuing green solution was added a solution (20 mM, 1 mL) of BiPy (0.02 mmol, 2 mol %) in acetonitrile transforming the colour to brown and back to green. After 6 min a solution (20 mM, 1 mL) of TEMPO (0.02 mmol, 2 mol %) in acetonitrile was added without any significant colour change. Finally, a solution (1 M, 40 μL) of DBU (0.04 mmol, 4 mol %) in acetonitrile was added transforming the colour to brown and gradually back to green. The reaction was stirred (500 rpm) under oxygen atmosphere (balloon) at room temperature. Samples (0.1 mL) were regularly taken and diluted with dichloromethane (1 mL) for GC analysis.

7.3.3.2 Typical oxidation experiment for allylic substrates with $CuBr_2$ (Table 7).

Geraniol **329** (1.54 g, 10.0 mmol, 100 mol %) was dissolved in acetonitrile (10 mL). Copper(II) bromide (0.067 g, 0.3 mmol, 3 mol %) was added followed by BiPy (0.047 g, 0.3 mmol, 3 mol %) transforming colour to brown and back to green. TEMPO (0.047 g, 0.3 mmol, 3 mol %) was added to the reaction mixture followed by *N*-methyl imidazole (0.049 g, 0.048 mL, 0.6 mmol, 6 mol %) giving brown solution. Slight exotherm was observed after reaction mixture was covered with oxygen balloon. Reaction was stirred at room temperature for one hour (GC showed >99% conversion). Appearance of blue solids and colour change of the solution to green was observed. Reaction mixture was partitioned between hexane (30 mL) and distilled water (30 mL). Aqueous phase was extracted with hexane (2 x 20 mL). Combined organic extracts were washed with aqueous 0.5 M H_3PO_4 –solution (30 mL), brine (30 mL), dried with anhydrous Na_2SO_4 and evaporated to dryness to afford 1.43 g (94%) of citral **330** as oil. No further purification was needed.[176]

7.3.3.3 Typical oxidation experiment for non-activated substrates with $Cu(OTf)_2$ (Table 8).

1-Decanol **350** (1.58 g, 10.0 mmol, 100 mol %) was dissolved in acetonitrile (10 mL). Copper(II) trifluoromethanesulfonate (0.108 g, 0.3 mmol, 3 mol %) was added followed by BiPy (0.047 g, 0.3 mmol, 3 mol %) to give blue solution. TEMPO (0.047 g, 0.3 mmol, 3 mol %) was added transforming colour to green. *N*-methyl imidazole (0.025 g, 0.024 mL, 0.3 mmol, 3 mol %) and DBU (0.046 g, 0.045 mL, 0.3 mmol,

3 mol %) were added giving brown solution. Reaction flask was covered with oxygen balloon. After 15 min 3 Å molecular sieves (1.5 g) were added. Reaction mixture was stirred at room temperature for 3 hours. Colour was transformed first to green and gradually to blue. Reaction mixture was filtered trough celite and partitioned between hexane (30 mL) and distilled water (30 mL). Aqueous phase was extracted with hexane (2 x 20 mL). Combined organic extracts were washed with aqueous 0.5 M H_3PO_4 –solution (30 mL), brine (30 mL), dried with anhydrous Na_2SO_4 and evaporated to dryness to afford 1.49 g (95%) of decanal **351** as oil. No further purification was needed.[176]

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176 This material is commercially available.

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