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Rearrangements to vinyl substituted hetero- and carbocycles

Total synthesis of siphonazole B and other applications in oxazole and saturated ringsynthesis

Paulsen, Filip

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Rearrangements to vinyl substituted hetero- and carbocycles

Total synthesis of siphonazole B and other
applications in oxazole and saturated ring
synthesis

Filip Paulsen



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LICENTIATE DISSERTATION

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| <p>Abstract</p> <p>The aim of this thesis is to explore and develop new reactions for rapid generation of molecular complexity. By enabling access to important molecules in a less wasteful and more cost-efficient manner such development benefits the whole modern society, where increasingly complex molecules are needed to solve problems within fields ranging from medicine, to materials sciences and the perfume industry.</p> <p>Reactions in which multiple bond-forming and -breaking events occur in a single step can be used to assemble large parts of target molecules such as natural products or pharmaceuticals in a reduced number of steps – saving time, energy, and raw materials needed to complete the desired synthesis. Within this realm we developed the first domino synthesis of 4-vinyl oxazoles by merging a cyclocondensation reaction with an unprecedented 1,2-oxazole rearrangement process. We studied the reaction mechanism by DFT-calculation and demonstrated its use within a concise synthesis of the cytostatic natural product siphonazole B.</p> <p>The last chapter of this thesis discuss the development of a new iridium-catalyzed skeletal rearrangement process. The reaction was enabled by the design of a iridacyclooctene with a large barrier for reductive elimination, and gives access to densely functionalized five-membered carbo and heterocycles from alkene-tethered vinylcyclopropanes.</p> | | |
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Total synthesis of siphonazole B and other
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2. von Wachenfeldt, H.; Paulsen, F.; Sundin, A.; Strand, D. "*Synthesis of Substituted Oxazoles from N-Benzyl Propargyl Amines and Acid Chlorides*" *Eur. J. Org. Chem.* **2013**, *2013*, 4578.
3. von Wachenfeldt, H.; Polukeev, A. V.; Loganathan, N.; Paulsen, F.; Rose, P.; Garreau, M.; Wendt, O. F.; Strand, D. "*Cyclometallated gold(iii) aryl-pyridine complexes as efficient catalysts for three-component synthesis of substituted oxazoles*" *Dalton Trans.* **2015**, *44*, 5347.



To you (if you want it)

Content

| | |
|--|----|
| Publications not included in this thesis:..... | 5 |
| Content | 8 |
| Acknowledgement | 10 |
| Abbreviations | 12 |
| Populärvetenskaplig sammanfattning | 13 |
| 1. Introduction | 14 |
| 1.1. Domino reactions – by virtue of the previous step | 15 |
| 1.2. Transition-metals enable new reactions | 17 |
| 1.3. Aim of this thesis | 18 |
| 2. Development of a cascade cyclocondensation/1,2-oxazole shift reaction | 19 |
| 2.1. Introduction | 19 |
| 2.2. Development of the cascade | 24 |
| 2.2.1. Initial considerations and experiments | 24 |
| 2.2.2. The 1,2-oxazole rearrangement reaction in isolation | 27 |
| 2.2.3. Tandem cyclocondensation/ 1,2-oxazole rearrangement | 30 |
| 2.2.4. Hypothesis and calculations on the mechanism | 32 |
| 2.3. Conclusions | 34 |
| 3. Synthesis of siphonazole B | 35 |
| 3.1. Introduction | 35 |
| 3.1.1. Prior art in the synthesis of the siphonzoles | 36 |
| 3.2. Retrosynthesis of siphonazole B | 38 |
| 3.2. The 7-8-9 steps to siphonazole B | 39 |
| 3.2.1. Fragment synthesis | 39 |
| 3.2.2. Fragment coupling | 42 |
| 3.2.3. Oxidative amidation and endgame | 43 |
| 3.3. Conclusions | 46 |
| 4. Iridium-catalyzed skeletal rearrangement | 47 |
| 4.1. Introduction | 47 |
| 4.2. Development of the skeletal rearrangement reaction | 49 |

| | |
|---|----|
| 4.2.1. Proof for the hypothesis of an alternative pathway..... | 49 |
| 4.2.2. Ir(cod) and other catalytic systems catalyze the reaction..... | 51 |
| 4.2.3. Heteroatom-tethered VCP-enes are tolerated to a lesser extent | 53 |
| 4.2.4. Labeling experiments corroborate the mechanistic hypothesis. | 54 |
| 4.3. Conclusions..... | 57 |
| 5. Conclusions | 58 |
| 6. Perspectives and future work | 59 |

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Abbreviations

| | |
|-------|--|
| BArF | Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate |
| BMIM | 1-Butyl-3-methylimidazolium |
| CAN | Ceric ammonium nitrate |
| cod | Cyclooctadiene |
| DABCO | 1,4-Diazabicyclo[2.2.2]octane |
| dbcot | Dibenzo[a,e]cyclooctatetraene |
| DCE | 1,2-Dichloroethane |
| DDQ | 2,3-Dichloro-5,6-dicyano- 1,4-benzoquinone |
| DFT | Density functional theory |
| DMA | Dimethylacetamide |
| DMAP | 4-Dimethylamino-pyridine |
| DMF | Dimethyl formamide |
| DMSO | Dimethyl sulfoxide |
| LDA | Lithium diisopropylamide |
| LPDE | Lithium perchlorate diethyl ether |
| NMP | <i>N</i> -methyl-pyrrolidone |
| PTSA | <i>p</i> -Toluenesulfonic acid |
| TBS | <i>tert</i> -Butyl silyl |
| TEMPO | 2,2,6,6-Tetramethylpiperidin-1-oxyl |
| TFE | 2,2,2-Trifluoroethanol |
| THF | Tetrahydrofuran |
| TIPS | Triisopropylsilyl |
| TMS | Trimethylsilyl |
| TPAP | Tetrapropylammonium perruthenate |

Populärvetenskaplig sammanfattning

Naturen är den största inspirationskällan för kemister, farmakologer, och andra forskare som vill utveckla nya substanser som färgämnen, läkemedel, eller parfymer. I svampar, växter, och bakterier hittar vi molekyler med mycket intressanta och varierande strukturer. Idag kan vi återskapa alla dessa molekyler i laboratorier och fabriker om tillräckligt med tid och resurser ges – men många av dessa molekyler är så komplexa att det vore opraktiskt att ens försöka. För bara femtio år sedan var situationen ännu svårare och få kemister hade vågat säga att det mesta är möjligt – men tack vare utvecklingen av nya reaktioner och en ständigt ökande förståelse för organisk kemi ser det idag mycket ljusare ut. Denna avhandling handlar om just det – att utveckla nya reaktioner som underlättar för kemister, som liksom alla andra har begränsat med tid och resurser, att göra komplexa molekyler på ett praktiskt sätt.

Kapitel två i denna avhandling handlar om utvecklingen av en ny metod för att tillverka 4-vinyloxazoler, en struktur som återfinns i många biologiskt aktiva molekyler som hittas i naturen. Genom att kombinera en metod för att tillverka oxazoler med en helt ny omlagringsreaktion där oxazolen flyttar sig ett steg i molekylen kunde vi få tillgång till dessa värdefulla molekyler i ett steg istället för flera, vilket kan spara både tid och resurser. Kapitel tre handlar om hur vi använde denna metod för att tillverka siphonazol B, en naturprodukt som hittades i en sorts bakterie och som har visat sig kunna minska tillväxten av både cancerceller och malariaparasiter.

I kapitel fyra diskuteras utvecklingen av en annan ny reaktion, en *skeletal omlagring*. Denna typ av reaktion omorganiserar bland atomerna i en molekyl för att ge en annan och mer komplex struktur som återfinns ibland annat läkemedel. Reaktionen möjliggjordes av en katalysatormolekyl gjord av metallen iridium, som kan snabba upp reaktioner som annars skulle ske för långsamt för att ens kunna observeras.

1. Introduction

We live in a time where the ease of access to the vast and ever increasing body of knowledge makes problem solving easier than ever before. Increased understanding of chemical and biological processes has allowed pharmacists and chemists to develop cures and treatments for conditions that would have been a death sentence in the 18th century. In the early 19th century, Mother Nature was the only source for medicines until the discovery of the synthetic sedative-hypnotic agent chloral hydrate in 1869.¹ Still today, Nature is a major source of inspiration for new medicines and other molecules. In principle any molecule created by her can be recreated in the laboratory using today's existing synthetic methodology given enough time and resources.

We can solve supply problems and expand on the existing structural space by synthetically producing molecules in the laboratory and in factories, but still today many molecules found in nature remain too complex to be reproduced in a practical way. Take the classical example of paclitaxel (Taxol). After a massive screening program started in 1960 it was found that the compound isolated from bark of the Pacific yew could be used to treat several different forms of cancer. However, a kilogram of the bark contains only milligrams of the active compound, and hundreds of thousands of trees would have to be sacrificed to offer Taxol to all Americans with ovarian cancer. The first total syntheses were completed in 1994,² two years after Taxol was approved for clinical use, yet after almost 20 years less than 30 mg totally synthetic paclitaxel had been added to the collective stock.³ Clearly, organic synthesis *can* be used to produce many complex molecules, but this example tells us that we have to continue developing synthetic methodology so as to make such syntheses practically useful – we need to be able to reach chemical complexity in simpler and more efficient ways. Luckily in this case, the Taxol problem could be solved by a combined

¹ Jones, A. W. "Early drug discovery and the rise of pharmaceutical chemistry" *Drug Test. Anal.* **2011**, 3, 337.

² Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S. "First total synthesis of taxol. I. Functionalization of the B ring" *J. Am. Chem. Soc.* **1994**, 116, 1597.

³ Mendoza, A.; Ishihara, Y.; Baran, P. S. "Scalable enantioselective total synthesis of taxanes" *Nat. Chem.* **2012**, 4, 21.

semisynthetic/microbiological method⁴ – obviously a broad interdisciplinary toolbox is needed to solve many problems and we have chosen to expand the organic synthetic part of that box.

So what is a practical synthesis? Paclitaxel syntheses were impractical as they required huge amounts of time and other resources to yield minute quantities of the desired compound. In nature this is done in an efficient and environmentally friendly manner as cells have access to reactions that directly build the complexity on already complex intermediates without going through unnecessary steps. Biosyntheses are often close to *ideal*, which Hendrickson defined as a synthesis that

“...creates a complex molecule...in a sequence of only construction reactions involving no intermediary refunctionalizations, and leading directly to the target, not only its skeleton but also its correctly placed functionality.”⁵

An ideal synthesis skips all the steps that don't directly form bonds that are present in the molecule such as protecting group manipulations or functional group interconversions and therefore selective reactions that directly establish the correct substitution patterns of e.g. heterocycles (skipping e.g. halogenation/substitution sequences) are required.

1.1. Domino reactions – by virtue of the previous step

Ideal or not, one way of conserving energy and other resources is to limit the number of steps or chemical operations required to reach a synthetic target. Thus the molecular complexity gained and the number of bonds that are broken and/or formed in each operation has to increase – which can be achieved by allowing several different reactions to occur directly after each other under the same reaction conditions.⁶

As defined by Tietze,⁷ such avalanche-like processes where each transformation occur under the same reaction conditions by virtue of bonds formed or broken in

⁴ Li, J. J. *Laughing gas, Viagra, and Lipitor: the human stories behind the drugs we use*; Oxford University Press: New York, 2006.

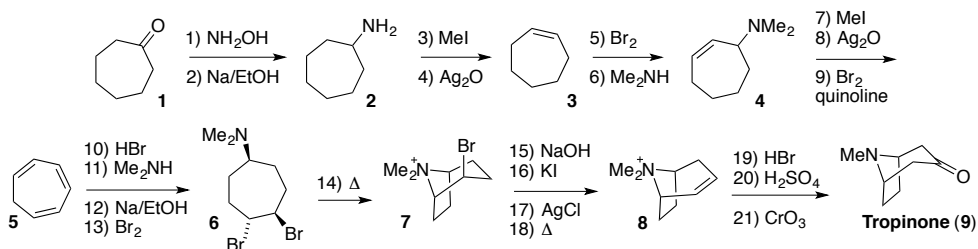
⁵ Gaich, T.; Baran, P. S. "Aiming for the Ideal Synthesis" *J. Org. Chem.* **2010**, 75, 4657.

⁶ Tietze, L. F.; Brasche, G.; Gericke, K. M. In *Domino Reactions in Organic Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: 2006.

⁷ Tietze, L. F. "Domino Reactions in Organic Synthesis" *Chem. Rev.* **1996**, 96, 115.

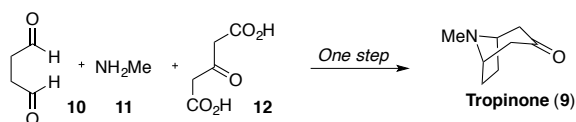
the previous step⁸ are called domino reactions. In some cases, an intermediate does not reach a steady-state concentration but is accumulated until the conditions are changed e.g. by an increase in temperature or by the addition of another reactant – then called tandem to consecutive or tandem sequential reactions, respectively. In any case, reduced waste and improved efficiency due to limited handling is often possible.

The merits of domino-processes was clearly demonstrated when the demand for the nerve-gas antidote atropine increased in the realms of world war I. Atropine was isolated from *Atropa Belladonna* or produced from tropinone, which was synthetically accessible through Willstatter's 21 step synthesis that gave only 0.75% yield from cycloheptanone.⁹



Scheme 1. Willstatter's synthesis of tropinone required 21 steps and delivered 0.75% yield.

In 1917, Robinson demonstrated the first rationally designed domino-reaction with his one-step synthesis of tropinone,¹⁰ which improved the efficiency to 43% (90% yield is now achievable through the optimized method). The method allowed the supply needs of atropine to be met by synthesis, and as it turned out the method was nearly identical to that employed by *Belladonna* itself – making the synthesis unintentionally bioinspired.⁹

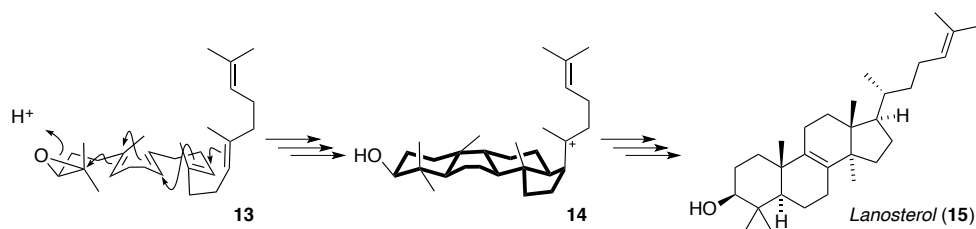


Scheme 2. Robinson's one-step synthesis of tropinone was developed in 1917, making it the first domino-synthesis.

⁸ Not considering formation of typical reactive intermediates such as carbocations.

⁹ Medley, J. W.; Movassaghi, M. "Robinson's landmark synthesis of tropinone" *Chem. Commun.* **2013**, 49, 10775.

¹⁰ Robinson, R. "LXIII.-A synthesis of tropinone" *J. Chem. Soc., Trans.* **1917**, 111, 762.



Scheme 3. The biosynthetic pathway to the steroid precursor lanosterol.

Clearly, nature has found a use for domino reactions in very efficient biosynthesis of highly complex molecules. A particularly illustrative example is the biosynthesis of steroids, as the cascade of reactions actually very closely resembles a game of domino, which has inspired chemists to develop similar cycloisomerization approaches for steroid synthesis and other polycyclic molecules.^{11,7}

1.2. Transition-metals enable new reactions

Transition-metal catalysis enables synthetic routes that would be impossible to design by simply using the intrinsic reactivity of organic functional groups. By enabling new “impossible” reactions, transition metal catalysis provides powerful methods to construct complex molecules.

The reactivity is distinct to that of classic organic reactions due to the transition metals incomplete d-subshell, which allows the metals to both accept and donate electrons – thus modulating the reactivity of coordinated organic molecules.¹² This also allows us to tweak the reactivity of such complexes by changing the electronic environment, either around the metal center by choosing different ligands, or by changing the actual metal or its oxidation state.¹³ By experimenting

¹¹ Thoma, R.; Schulz-Gasch, T.; D'Arcy, B.; Benz, J.; Aebi, J.; Dehmlow, H.; Hennig, M.; Stihle, M.; Ruf, A. "Insight into steroid scaffold formation from the structure of human oxidosqualene cyclase" *Nature* **2004**, 432, 118.

¹² Spessard, G. O.; Miessler, G. L. *Organometallic Chemistry*; Oxford University Press: New York, 2010.

¹³ Crabtree, R. H. In *The Organometallic Chemistry of the Transition Metals*; John Wiley & Sons, Inc.: 2005.

with this we can tailor known reactions to our needs, or even develop completely new reactions.

1.3. Aim of this thesis

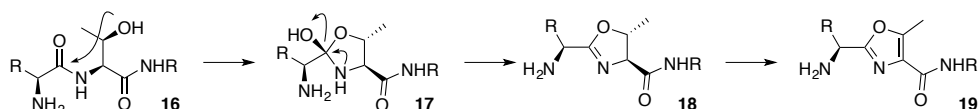
As increasingly complex molecules are needed to solve problems in the fields of medicine, materials science, and electronics the organic chemist have to rely on an expanding toolbox of methods to use. We aspire to expand on the methods available to by developing new complexity generating reactions that simplify access to molecules that would otherwise require long, impractical, or environmentally harsh methods to be made. By doing this, we hope to not only contribute to a growing toolbox of reactions, but also to improve understanding of the processes involved. Therefore – the aim of this thesis is to develop new interesting chemical reactions that rapidly generate complexity from simpler materials.

Chapter 2 of this thesis deals with the development of a direct synthesis of 4-vinyl oxazoles from acyclic precursors through a domino cyclocondensation/1,2-oxazole rearrangement process. Chapter 3 demonstrates its use in a total synthesis of the natural product siphonazole B. Chapter 4 discusses the early development of an iridium catalyzed skeletal rearrangement process that gives access to densely functionalized saturated five membered carbo- and heterocycles from alkene-tethered vinylcyclopropanes.

2. Development of a cascade cyclocondensation/1,2-oxazole shift reaction

2.1. Introduction

Oxazoles are prevalent natural products commonly found in microorganisms, of both terrestrial and marine origin.¹⁴ Biosynthetically, they are commonly made by dehydration of peptides containing serine or threonine residues catalyzed by non-ribosomal peptide synthetases¹⁵ leading to some recurrent structural features in many of the molecules they constitute. For example, the oxazole 5-position is often unsubstituted – containing only a hydrogen atom if the heterocycle originates from a serine residue, or a methyl group if it originates from threonine as shown in Scheme 4. Furthermore, the 2- and 4- positions of the oxazoles are often substituted with a carboxyl group originating from other remaining parts of the peptide chain and sometimes these are converted to 2- and 4-vinyl oxazoles by polyketide synthetases.¹⁶



Scheme 4. The general mechanism for biosynthesis of oxazoles.

As shown in Figure 1, many of these oxazole-natural products display significant biological effects and include potent antibacterial and antiviral agents as well as

¹⁴ Jin, Z. "Muscarine, imidazole, oxazole and thiazole alkaloids" *Nat. Prod. Rep.* **2016**, *33*, 1268.

¹⁵ Hemmerling, F.; Hahn, F. "Biosynthesis of oxygen and nitrogen-containing heterocycles in polyketides" *Beilstein J. Org. Chem.* **2016**, *12*, 1512.

¹⁶ Kopp, M.; Irschik, H.; Pradella, S.; Müller, R. "Production of the Tubulin Destabilizer Disorazol in *Sorangium cellulosum*: Biosynthetic Machinery and Regulatory Genes" *ChemBioChem* **2005**, *6*, 1277.

tumor and immune-suppressive compounds.¹⁴ In fact, one of the most potent cytostatic agents known is a dual vinyl-oxazole, phorboxazole, which inhibits growth of cancer cells at picomolar concentrations.¹⁷

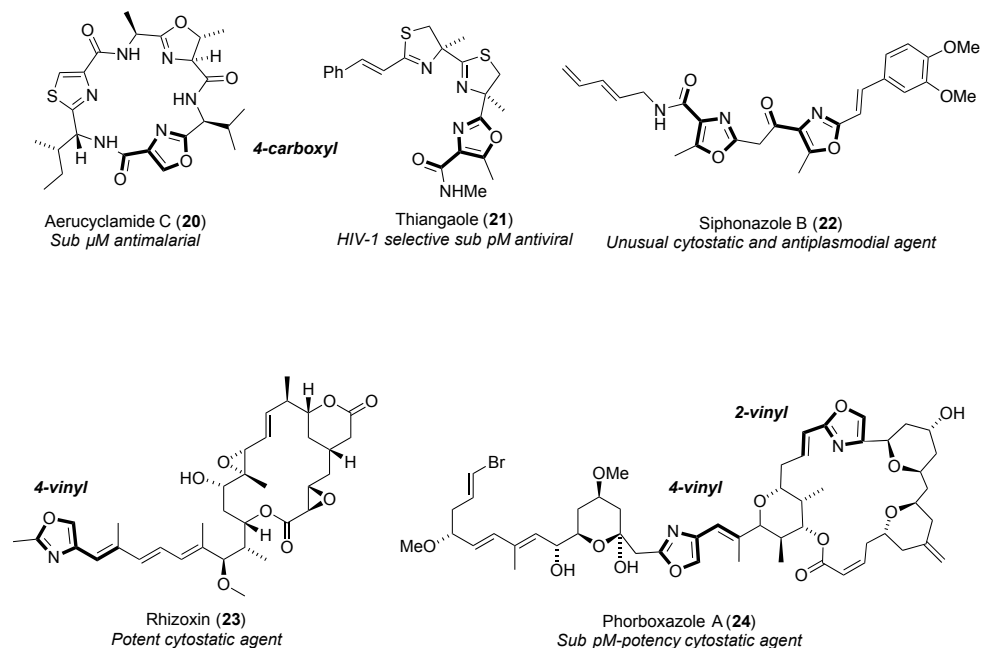


Figure 1. The structurally diverse oxazole-containing natural products exhibit various different biological effects. See references; (20)¹⁸, (21)¹⁹, (22)²⁰, (23)²¹ and (24)¹⁷.

Several methods are established and used for the synthesis of oxazoles,^{22 23} one of the oldest and most widely used methods for synthesis of 4-carboxyl oxazoles –

¹⁷ Searle, P. A.; Molinski, T. F. "Phorboxazoles A and B: potent cytostatic macrolides from marine sponge *Phorbas species*" *J. Am. Chem. Soc.* **1995**, *117*, 8126.

¹⁸ Portmann, C.; Blom, J. F.; Kaiser, M.; Brun, R.; Jüttner, F.; Gademann, K. "Isolation of *Aerucyclamides C and D* and Structure Revision of *Microcyclamide 7806A*: Heterocyclic Ribosomal Peptides from *Microcystis aeruginosa* PCC 7806 and Their Antiparasite Evaluation"

¹⁹ Parsons, R. L.; Heathcock, C. H. "Total Synthesis of (-)-Thiangaole, a Naturally-Occurring HIV-1 Inhibitor" *J. Org. Chem.* **1994**, *59*, 473

²⁰ Nett, M.; Erol, Ö.; Kehraus, S.; Köck, M.; Krick, A.; Eguereva, E.; Neu, E.; König, G. M. "Siphonazole, an Unusual Metabolite from *Herpetosiphon sp*" *Angew. Chem. – Int. Ed.* **2006**, *45*, 3863.

²¹ Tsuruo, T.; Oh-hara, T.; Iida, H.; Tsukagoshi, S.; Sato, Z.; Matsuda, I.; Iwasaki, S.; Okuda, S.; Shimizu, F.; Sasagawa, K.; Fukami, M.; Fukuda, K.; Arakawa, M. "Rhizoxin, a Macrocyclic Lactone Antibiotic, as a New Antitumor Agent against Human and Murine Tumor Cells and Their Vincristine-resistant Sublines" *Cancer Res.* **1986**, *46*, 381.

the Robinson-Gabriel synthesis,²⁴ is conceptually similar to the biosynthetic pathway. It involves dehydration of 2-acylaminoketones (i.e. oxidized serine derivatives) with Lewis or Brønsted acid catalysis. Another important method is based on direct catalytic cycloadditions of diazocarbonyl compounds with nitriles or amides – a variation of earlier known cycloadditions to carbenes²⁵ made practical by Helquist *et al.* in 1986.²⁶

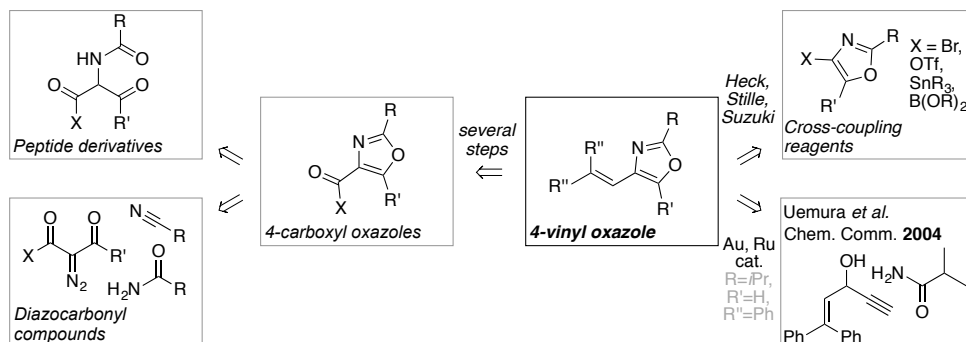


Figure 2. Different methods to access 4-carboxyl and 4-vinyl oxazoles.

²² Joule, J. A.; Mills, K. *Heterocyclic Chemistry*; John Wiley & Sons: Auflage, 2010.

²³ Palmer, D. C.; Venkatraman, S. In *Oxazoles: Synthesis, Reactions, and Spectroscopy, Part A*; John Wiley & Sons, Inc.: 2003

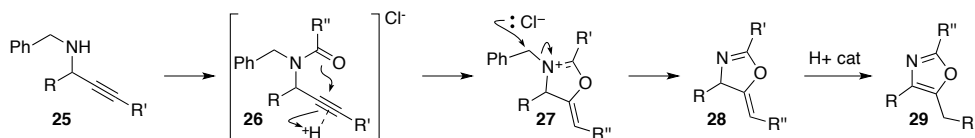
²⁴ Robinson, R. "CCXXXII.-A new synthesis of oxazole derivatives" *J. Chem. Soc. Trans.* **1909**, 95, 2167.

²⁵ Turchi, I. J.; Dewar, M. J. S. "Chemistry of oxazoles" *Chem. Rev.* **1975**, 75, 389.

²⁶ Connell, R.; Scavo, F.; Helquist, P.; Åkermark, B. "Functionalized oxazoles from rhodium-catalyzed reaction of dimethyl diazomalonate with nitriles" *Tet. Lett.* **1986**, 27, 5559.

4-vinyl oxazoles are usually made either by conversion of 4-carboxyl-oxazoles,²⁷ or via cross-coupling methods.^{23,28} There is no general method for the synthesis of 4-vinyl oxazoles by ring-formation, but sporadic examples are reported, including a gold and ruthenium catalyzed sequential propargylic substitution/cyclization to yield a diphenyl-vinyl-oxazole,²⁹ and a rhodium-catalyzed addition/cyclization of styryl-diazoacetates and oximes.³⁰

We have previously disclosed two new methods for efficient general synthesis of oxazoles, both involving a cyclocondensation step enabled by the use of a *N*-benzyl group as an electrofuge. In its simplest form as shown in Scheme 5, the reaction manifold is initiated when an acyl chloride is added to an *N*-benzyl propargylamine. The HCl released in the acylation step activates the alkyne for 5-exo-dig cyclization with the amide. This gives rise to an oxazolinium cation, which formally loses a Bn⁺, liberating the oxazoline that isomerizes to give the aromatic oxazole.³¹



Scheme 5. Cyclocondensation of propargylamines to oxazoles is enabled by the use of a benzyl group as a pendant electrofuge.

When combined with the transition metal catalyzed addition of alkynes to imines (a part of the popular A³-multicomponent reaction cascade³²) the oxazoles could be obtained directly in a multicomponent cascade involving non-enolizable imines, alkynes, and acyl chlorides.

²⁷ Zhao, Z.; Scarlato, G. R.; Armstrong, R. W. "Synthesis of *trans*-4-alkenyl oxazoles" *Tet. Lett.* **1991**, 32, 1609.

²⁸ Schnürch, M.; Flasiak, R.; Khan, A. F.; Spina, M.; Mihovilovic, M. D.; Stanetty, P. "Cross-Coupling Reactions on Azoles with Two and More Heteroatoms" *Eur. J. Org. Chem.* **2006**, 2006, 3283.

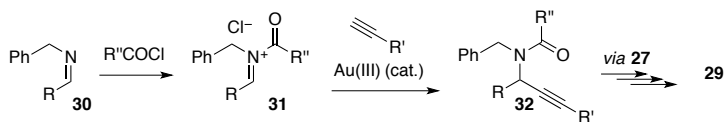
²⁹ Milton, M. D.; Inada, Y.; Nishibayashi, Y.; Uemura, S. "Ruthenium- and gold-catalysed sequential reactions: a straightforward synthesis of substituted oxazoles from propargylic alcohols and amides" *Chem. Commun.* **2004**, 2712.

³⁰ Xu, X.; Zavalij, P. Y.; Hu, W.; Doyle, M. P. "Efficient synthesis of oxazoles by dirhodium(II)-catalyzed reactions of styryl diazoacetate with oximes" *Chem. Commun. (Camb.)* **2012**, 48, 11522.

³¹ v. Wachenfeldt, H.; Paulsen, F.; Sundin, A.; Strand, D. "Synthesis of Substituted Oxazoles from *N*-Benzyl Propargyl Amines and Acid Chlorides" *Eur. J. Org. Chem.* **2013**, 2013, 4578.

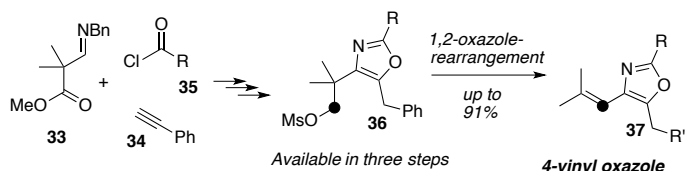
³² Peshkov, V. A.; Pereshivko, O. P.; Van der Eycken, E. V. "A walk around the A³-coupling" *Chem. Soc. Rev.* **2012**, 41, 3790.

The latter reaction was limited to quaternary aliphatic imines, which limited the scope of oxazoles available to those with tert-butyl and similar substituents in the 4-position. When investigating ways around this limitation we discovered the first 1,2-oxazole rearrangement reaction – a highly unusual Wagner-Meerwein type rearrangement reaction.³³ Remarkably, despite its mechanism has been known since the early 20th century,³⁴ only a few examples are known wherein the migrating group is a heteroaromatic entity.



Scheme 6. A combination of the cyclocondensation protocol and alkyne-imine addition enabled a three-component gold catalyzed domino synthesis of oxazoles.

The few examples of such processes known in the literature include oxidative 1,2-rearrangements with different heterocyclic migrating groups yielding (hetero)-aryl acetates³⁵ from acetophenones mediated by iodic acid, or (hetero)-aryl-malonates³⁶ from propargyl alcohols catalyzed by gold. Examples are also known involving solvolytic 1,2-rearrangements of indoles³⁷ and imidazoles³⁸ – the latter being reported as an undesired side reaction only.



Scheme 7. Our multicomponent approach to oxazoles enabled three-step access to mesylate **36**, which underwent a remarkable 1,2-oxazole rearrangement upon heating.

³³ v. Wachenfeldt, H.; Röse, P.; Paulsen, F.; Loganathan, N.; Strand, D. "Catalytic Three-Component Domino Reaction for the Preparation of Trisubstituted Oxazoles" *Chem. Eur. J.* **2013**, *19*, 7982.

³⁴ Meerwein, H. "Über den Reaktionsmechanismus der Umwandlung von Borneol in Camphen; [Dritte Mitteilung über Pinakolinumlagerungen.]" *Liebigs Ann.* **1914**, *405*, 129.

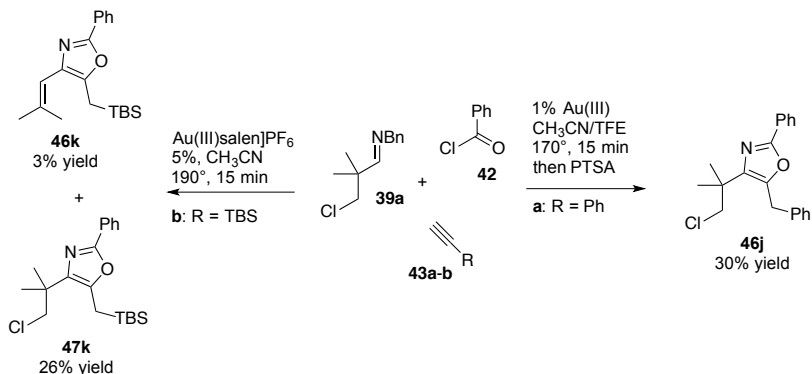
³⁵ Akamachi, K. G.; Hudda, S. N.; Deshmukh, S. S. "Oxidative rearrangement of alkyl aryl /heteroaryl ketones by 1,2-aryl/heteroaryl shift using iodic acid" *Arkivoc* **2011**, 67.

³⁶ Yao, X.; Wang, T.; Zhang, X.; Wang, P.; Zhang, B.; Wei, J.; Zhang, Z. "One-Pot Synthesis of 4-Heteroaryl-Substituted Pyrazoles: A Gold-Catalyzed Oxidation/1,2-Heteroaryl Migration Cascade Constitutes the Key Step" *Adv. Synth. Catal.* **2016**, *358*, 1534.

³⁷ Ritchie, R.; Saxton, J. E. *J. Chem. Res. Synop.* **1990**, 48

³⁸ Korakas, P.; Chaffee, S.; Shotwell, J. B.; Duque, P.; Wood, J. L. "Efficient construction of the securine A carbon skeleton" *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12054.

the desired rearrangement product was observed when the reaction was run at 190 °C. Attempts to promote the rearrangement step by running the reactions at higher temperatures and for longer reaction times were only moderately successful. The uninspiring results led us to consider a simpler process involving a preformed propargyl amine in a cyclocondensation/1,2-rearrangement cascade instead.



Scheme 9. β -chloro-imine **39a** was tolerated in the three-component oxazole synthesis, but only moderate yields were obtained.

Addition of lithiated silyl acetylenes or sodium acetylide to imine **39a** were unproductive under various conditions even at elevated temperatures and with various Lewis-acids added, as were traditional A³-coupling-type protocols using gold or copper catalysis.

We have previously successfully used Carreira's protocol for the synthesis of silyl-protected propargylamines, wherein a silyl acetylene is added to an imine under iridium catalysis.⁴⁰ An improved protocol including a catalytic amount of MgI₂⁴¹ allowed the synthesis of **44** on a 10 g scale using less than 1.5 mol% [Ir(cod)Cl]₂ followed by deprotection in the same vessel to yield the simplest possible propargylamine for use in further reactions in 95% yield.

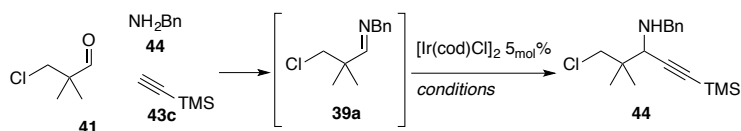
Iridium catalyzed variations of the A³-coupling were problematic, possibly due to the presence of the free primary amine during the imine-formation step. Attempts to perform the reaction with slow addition of the various components in different orders via syringe-pump were unsuccessful. Various other parameters were also

⁴⁰ Fischer, C.; Carreira, E. M. "Direct Addition of TMS-acetylene to Aldimines Catalyzed by a Simple, Commercially Available Ir(I) Complex" *Org. Lett.* **2001**, 3, 4319.

⁴¹ Fischer, C.; Carreira, E. M. "MgI₂ as an Additive in Ir(I)-Catalyzed Addition of Silylacetylenes to Imines: Expedient Synthesis of Propargylic Amines" *Synthesis* **2004**, 2004, 1497.

optimized to increase conversion from the aldehyde starting material and imine intermediate to the desired propargylamine as shown in table 1.

Table 1. A³-type synthesis of propargylamine **44**.



| Solvent | Additive | T /°C | t /h | Slow add ^a | 41:39a:44 ^b /% |
|---------------------------------|--|-------|------|-----------------------|---------------------------|
| Et ₂ O | MgI ₂ (20%), LiClO ₄ (5 M) | RT | 24 | - | - : - : 59 (isol) |
| THF | MgI ₂ (20%) | 60 | 24 | Precat. | 9:12:47 |
| THF | MgI ₂ (20%) | 60 | 24 | Amine | 15:50:7 |
| THF | MgI ₂ (20%) | 60 | 24 | Amine+alkyne | 15:23:30 |
| THF | MgI ₂ (20%) | 60 | 24 | Aldehyde | 21:38:10 |
| THF | LiClO ₄ (20 equiv.) | RT | 24 | - | ~10% conv. |
| CH ₂ Cl ₂ | LiClO ₄ (20 equiv.) | RT | 24 | - | ~10% conv. |
| Et ₂ O | LiClO ₄ (5 M/ 40 equiv.) | RT | 24 | - | ~10% conv. |
| Et ₂ O | LiClO ₄ (20 equiv.) | RT | 24 | - | ~10% conv. |

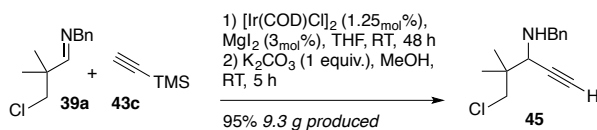
^a Reagents/catalyst were added as a solution in THF over 10 h by syringe pump. ^b NMR-yields.

General procedure: To a solution of [Ir(cod)Cl]₂ (8 mg, 12 μmol) in the specified solvent (2 ml) was added aldehyde **41** (30 mg, 0.25 mmol), followed by TMS-acetylene (55 μl, 0.39 mmol), followed by benzylamine (27 μl, 0.25 mmol). The reaction mixtures were stirred for the specified time and temperature, then the yields were measured by NMR using mesitylene as an internal standard, employing a 24 s relaxation delay.

Additives such as Lewis or Brønstedt-acids were unproductive at best, as were desiccants, other solvents, and temperatures (results not shown). However, when the reaction was run in the untraditional “solvent” LPDE (Lithium Perchlorate in Diethyl Ether, 5 M)⁴² significantly improved conversion was observed. This could be attributed to the mild Lewis-acidity of Li⁺, and possibly to the dessicant effect of such a high concentration of a salt in a non-polar solvent.

Despite adding a step to the synthesis, preformation of the imine was more practical on large scale – with Carreira’s original MgI₂-assisted protocol propargylamine **45** was routinely made on 10 g scale in >95% yield using only 1.25% [Ir(cod)Cl]₂ in a single pot.

⁴² R. Saidi, M.; Javanshir, S.; M. Mojtahedi, M. "Lithium Perchlorate Mediated Three Component Reaction for the Preparation of Primary Amines" *J. Chem. Res. Synop.* **1999**, 330.



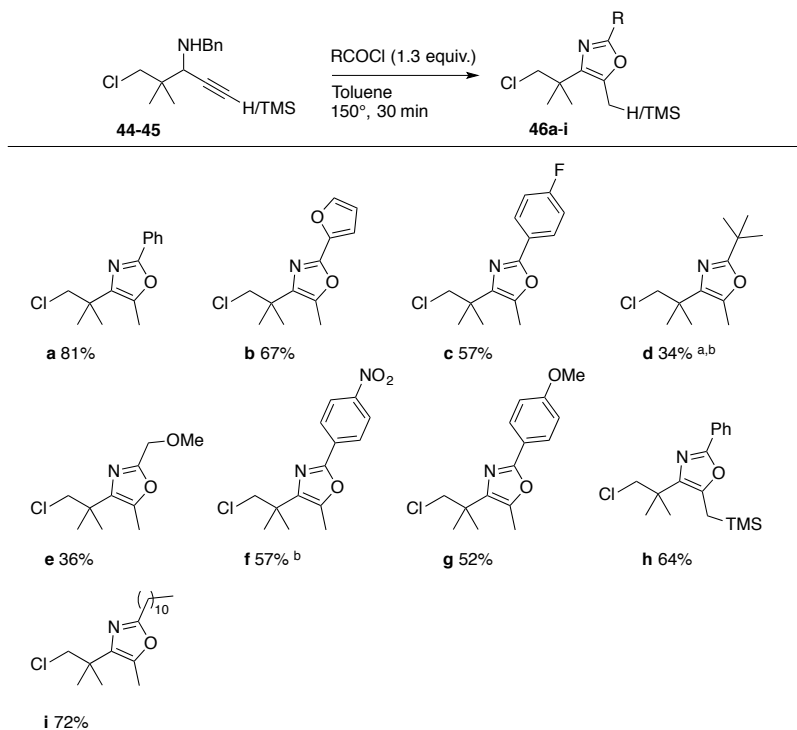
Scheme 10. Efficient, scalable preparation of propargylamine **45** was achieved in a single pot using Carreiras MgI_2 -enhanced, iridium catalyzed alkyne-imine coupling.

With simple access to decagram quantities of **45** we could set out to synthesize β -chloro-oxazoles and investigate the rearrangement reaction further.

2.2.2. The 1,2-oxazole rearrangement reaction in isolation

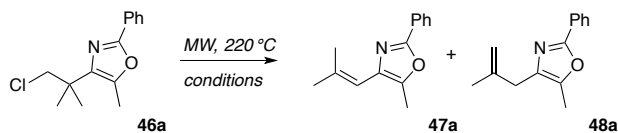
To investigate the 1,2-oxazole rearrangement using chloride as the leaving group, a series of β -chloro-oxazoles **46a-i** were synthesized using the propargylamine-cyclization method we have previously disclosed with some re-optimization for the chloro-propargylamine substrate.³¹ Thus, a series of β -chloro-oxazoles were synthesized in good to moderate yields by heating **44** or **45** with the corresponding acyl chloride in toluene as shown in Table 2.

Table 2. Synthesis of β -chloro-oxazoles by cyclocondensation of propargylamines **44** and **45** with acyl chlorides.



^a 2.3 equiv. pivaloyl chloride was used and reaction time was 95 min. ^b THF was used as the solvent.

Heating does not promote rearrangement of the β -chloro-oxazoles in non-polar solvents such as toluene or DCE, but the more polar acetonitrile and NMP both enabled the reaction at 220°C if the concentration was sufficiently high as shown in Table 3. This prompted us to investigate various Lewis-basic additives such as phosphines and amines. As shown in Table 3, in the presence of triphenylphosphine the rearrangement reaction proceeded to full conversion at shorter reaction times and with higher yields, suggesting involvement of some cationic transition state.

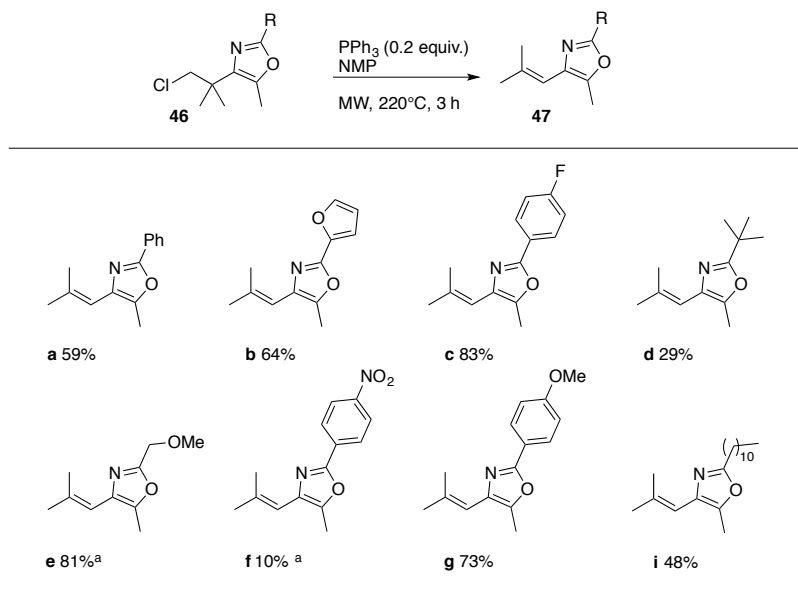
Table 3. Rearrangement of **46a** under various conditions.

| Solvent (conc./M) | Additive (equiv.) | t | 48 yield/% | 47 yield/% |
|---------------------------|------------------------------|------------|------------|-----------------|
| NMP (0.8) | PPh₃ (0.2) | 3 h | n.d. | 74 |
| NMP (0.77) | PPh ₃ (0.1) | 4 h | n.d. | 66 |
| NMP (0.8) | - | 3 h | 32 | 64 |
| NMP (1.3) | PPh ₃ (0.2) | 3 h | n.d. | 58 |
| CH ₃ CN (0.14) | PPh ₃ (0.2) | 7 h | n.d. | 58 ^a |
| CH ₃ CN (0.5) | PPh ₃ (0.2) | 4 h | n.d. | 57 ^a |
| CH ₃ CN (0.8) | - | 3 h | 23 | 56 |
| NMP (0.4) | PPh ₃ (0.2) | 3 h | n.d. | 51 ^a |
| CH ₃ CN (0.08) | - | 3 h | n.d. | n.d. |
| NMP (0.14) | - | 1 h | n.d. | n.d. |

Reactions were performed by heating approx. 0.5- 1 ml of a solution of **46a** and the appropriate additive in a closed vial by microwave irradiation. Yields were measured by NMR using mesitylene as an internal standard employing a >20 s relaxation delay. ^aIsolated yields.

Up to 74% yield was observed in NMP at 0.8 M with 0.2 equiv. PPh₃, which was the highest concentration investigated due to the more convenient purification. These conditions were then used to investigate the scope of the rearrangement reaction as shown in Table 4 below.

Intrestingly, 2-aryloxazoles with inductively electron donating substituents in the benzene-ring seem to promote the highest yields in the reaction (**c** and **g**), while oxazole **f** with the electron withdrawing nitrophenyl-substituent gave only 10% yield. This further corroborates our hypothesis on the involvement of a cationic transition-state in the reaction.

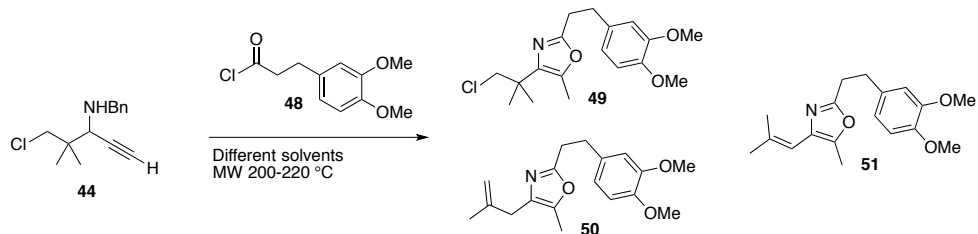
Table 4. 1,2-oxazole rearrangement of chloro-oxazoles **46a-i**.

Reactions were performed by heating a measured amount of chloro-oxazole in NMP at approximately 0.8 M in a closed vial by microwave irradiation. Yields are reported for isolated compounds after chromatography. ^aYields were measured by NMR using mesitylene as an internal standard employing a >20 s relaxation delay.

With a better understanding of the 1,2-oxazole rearrangement reaction, we now continued to study the possibility for running both the cyclocondensation reaction and 1,2-rearrangement simultaneously in a domino-process to further facilitate access to 4-vinyl oxazoles directly from acyclic precursors.

2.2.3. Tandem cyclocondensation/ 1,2-oxazole rearrangement

In order to run the rearrangement and cyclocondensation reactions in a domino-sequence, NMP was unsuitable as solvent as it promoted the formation of by-products, presumably through reaction with the acyl chloride. Other highly polar solvents such as DMSO, DMA, DMF, MeNO_2 and $(\text{MeO})_3\text{PO}$ also promoted side reactions when using the sensitive acyl chloride **48**, and CH_3CN was found to be the best alternative, which delivered the siphonazole-related oxazole **51** in 49% yield after 1.5 h at 220°C . In the presence of PPh_3 , the reaction time could be reduced to 20 min. DABCO was also found to shorten the reaction time, albeit with a slight decrease in yield compared to PPh_3 , but DMAP was found to be too reactive and only delivered **51** in 19% yield as shown in table 5.

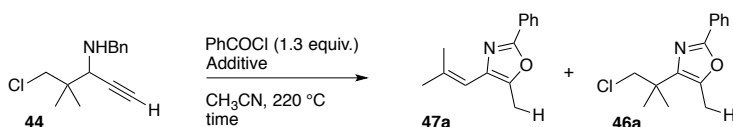
Table 5. Screening of conditions for the vinyl-oxazole forming cascade reaction.

| Solvent | Additive (equiv.) | T /°C | Time | 51 yield | Comments |
|--|------------------------------|------------|------------|------------------|-----------------|
| CH₃CN | PPh₃ (0.4) | 220 | 1 h | 59% | 4% 50 |
| CH ₃ CN | PPh ₃ (0.4) | 220 | 40 min | 55% | 3% 50 |
| CH ₃ CN | PPh ₃ (0.4) | 220 | 20 min | 55% | 5% 50 |
| CH ₃ CN | PPh ₃ (0.2) | 220 | 45 min | 50% | 4% 50 |
| CH ₃ CN | PPh ₃ (1.0) | 220 | 20 min | 50% | |
| CH ₃ CN | DABCO (0.5) | 220 | 50 min | 41% | 9% 49 + 5% 50 |
| CH ₃ CN | (MeO) ₃ PO (0.2) | 220 | 1 h | 43% | 10% 49 |
| CH ₃ CN | DMAP (1.1) | 215 | 1 h | 19% ^a | |
| Dioxane | PPh ₃ (0.4) | 220 | 1 h | n.d. | Only 49 |
| CH ₃ CN | - | 220 | 1.5 h | 49% | - |
| CH ₃ CN:(MeO) ₃ PO 4:1 | - | 220 | 1 h | n.d. | Decomp. |
| MeNO ₂ | - | 200 | 4 h | 29% | 10% 49 + 12% 50 |
| MeNO ₂ | - | 220 | 1.5 h | 15% | 20% 49 |
| EtOAc | - | 220° | 1.5 h | n.d. | 68% 49 |
| BMIM PF ₆ | - | 150 | 4 h | 15% | 24 % 49 |
| DMF | - | 220 | 1 h | 23% | 35% 50 |
| NMP | - | 220 | 1 h | 11% | 35 % 49 |
| DMSO | - | 220 | 8 min | n.d. | Decomp. |
| DMSO | - | 180 | 1 h | n.d. | No rxn. |
| Toluene | - | 220 | 1.5 h | n.d. | Only 49 |

Reactions were run on 50 mg scale with 1.1 equiv. acyl chloride in 0.5 ml of solvent and heated in closed vials by microwave irradiation. Yields were determined by NMR employing a 20 s repetition delay using DMF as an internal standard (mesitylene was used when DMF was the solvent). Reactions with additives were evaporated from MeOH prior to addition of the internal standard.^a Isolated yield.

In the table above, yields are reported for vinyl, allyl, and β -chloro oxazoles without consideration to demethylation or other side-reactions to the aryl side-chain. I.e. only the efficiency of the oxazole-formation and rearrangement steps are discussed and the yields could in fact be lower than reported.

When applied to the simpler system using benzoyl chloride as the acyl source, up to 65% NMR-yield, with an additional 7% of the intermediate chlorooxazole could be obtained with 1.05 equiv PPh₃ as an additive. It appears that higher reaction concentrations, as well as higher concentrations of PPh₃ generally lead to higher yields and shorter reaction times as shown in Table 6.

Table 6. Domino cyclocondensation/1,2-oxazole rearrangement to 2-phenyloxazole **47a**-

| Solvent (conc./M) | Add. (equiv.) | Time | 47a yield /% | 46a yield /% |
|---------------------------|-------------------------|-------|--------------|--------------|
| CH ₃ CN (1.0) | PPh ₃ (1.05) | 1 h | 65 | 7 |
| CH ₃ CN (1.0) | PPh ₃ (0.55) | 1 h | 56 | 12.5 |
| CH ₃ CN (1.0) | PPh ₃ (1.05) | 0.5 h | 47 | 25 |
| CH ₃ CN (0.85) | PPh ₃ (0.2) | 3 h | 41 | 0 |
| CH ₃ CN (1.0) | PPh ₃ (0.2) | 2.5 h | 37 | 4 |
| CH ₃ CN (0.85) | PPh ₃ (0.5) | 2 h | 23 | 0 |
| CH ₃ CN (0.85) | - | 6 h | 26 | 0 |

Reactions were run on 120 mg scale in 0.5-0.6 ml CH₃CN and heated in closed vials by microwave irradiation. Yields were measured by NMR using mesitylene as internal standard, employing a relaxation delay of 20 s.

The origin of the phosphine effect is unknown, but could be related to its nucleophilic/Lewis-basic properties. As more polar (Lewis basic) solvents also promote the rearrangement reaction, it could be related to some cation-stabilizing effect.

2.2.4. Hypothesis and calculations on the mechanism

We hypothesize that the rearrangement reaction occurs through a Wagner-Meerwein type reaction, either undergoing a concerted rearrangement/elimination mechanism, or through initial formation of a rearranged cationic intermediate as shown in Scheme 11. In either case, the reaction would be initiated by rupture of the C-Cl bond.

To find a plausible transition state for the reaction we performed DFT energy minimizations on the simple chlorooxazole **51**. Gradual elongation of the C-Cl bond led to the simultaneous formation of a new bond constituting the anticipated cyclopropane intermediate. The ΔG^\ddagger barrier for formation of this cationic intermediate was found to be 25 kcal/mol as shown in Diagram 1.⁴³ This

⁴³ DFT calculations were performed in ORCA on the B97-D3BJ-level employing a Def2-SV(P)-basis set on all atoms except oxazole-C₄, the carbon atom in the CH₂-group, and the chlorine atom for which a ma-Def2-TZVP(-f)-basis set was employed. Preliminary results have been obtained for the elimination step, which has a much lower activation energy of <10 kcal/mol, further studies are underway and will be reported in due course. For a benchmark comparison of different basis sets, see: Goerigk, L.; Grimme, S. "A thorough benchmark of density functional methods for general main group thermochemistry, kinetics, and noncovalent interactions" *Phys. Chem. Chem. Phys.* **2011**, *13*, 6670.

corroborates our hypothesis that the reaction is assisted by participation of the oxazole ring in a phenonium-ion like intermediate.

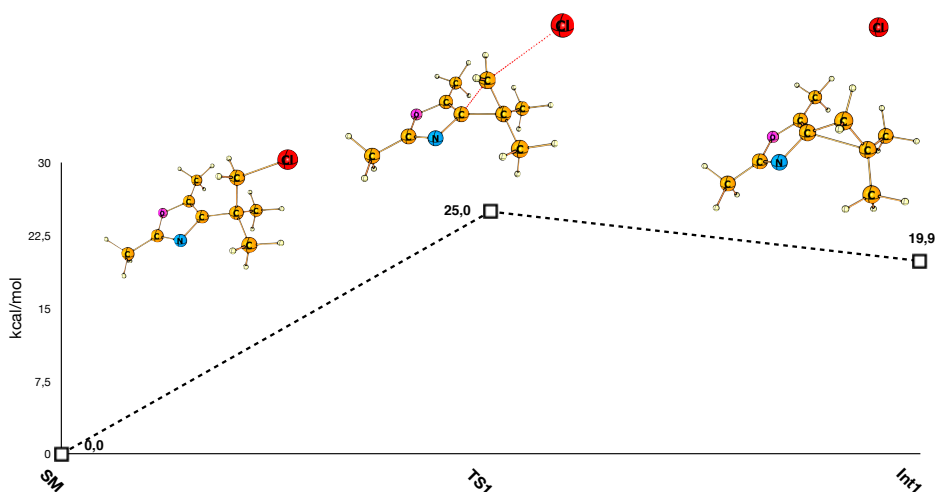
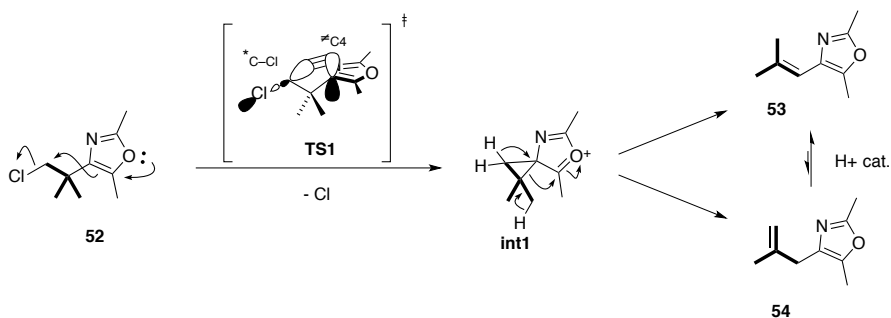


Diagram 1. Calculated Gibbs-free energies for the conversion of chloro-oxazole **52** into cationic intermediate **int1**.

The mechanism is also corroborated to some extent by the fact that it occurs only in polar cation-stabilizing solvents, which suggest that the rate-determining step involves cation formation.



Scheme 11. Proposed mechanism for the 1,2-oxazole rearrangement reaction involving anchimeric assistance by the oxazole ring, leading to intermediate **int1**.

While the calculations and experimental observations lends confidence to the mechanism proposed in Scheme 11, it is still unclear whether elimination can occur directly to the vinyl oxazole. Formation of allyl-oxazoles and their

conversion into vinyl oxazoles have been observed during the rearrangement reactions, thus it is likely that both alternatives are possible.

2.3. Conclusions

In conclusion, we have developed the first domino synthesis of 4-vinyl oxazoles from acyclic propargylamines. The reaction involves an unprecedented 1,2-oxazole shift, which is suggested by calculations to occur through a mechanism involving anchimeric assistance by the electron-rich oxazole leading to a phenonium-ion like intermediate. The reaction gives direct access to biologically relevant 4-vinyl oxazoles from acyclic and readily available starting materials.

3. Synthesis of siphonazole B

3.1. Introduction

The siphonazoles is an intriguing class of antiplasmodial and cytostatic natural products that were first isolated from a marine bacterium of the *Herpetosiphon* genus by König in 2006.²⁰ Their structures comprise two 4-carboxyl oxazole cores – commonly found in marine natural products, but here uniquely arranged with a two-carbon bridge separating them. Additional features include an unprecedented amide sidechain and the unusual oxazole-stilbene.

From a biosynthetic point of view, the siphonazoles are highly interesting. As explained above, oxazoles are produced in living organisms through cyclization of peptides by so-called non-ribosomal peptide synthetases that are only present in bacteria. This makes the two-carbon tether unusual as cyclization within a normal oligo-peptide only would allow formation of directly linked oxazoles, or oxazoles separated by three or more atoms. Furthermore, as bacteria very rarely contain phenylalanine-deaminases,⁴⁴ cinnamic acid derivatives like that part of the oxazole stilbene are unusual in bacterially produced secondary metabolites.⁴⁵ Lastly, the pentadienyl-amide side chain has never before been observed in a natural product.

This unusual structure sparked an interest among the organic synthetic community and the groups of Moody,⁴⁶ Ciufolini,⁴⁷ and Ley⁴⁸ have all developed total

⁴⁴ Hemmati, S. "Phenylalanine ammonia-lyase through evolution: A bioinformatic approach" *Trends Pharm. Sci.* **2015**, *1*, 10.

⁴⁵ Bode, H. B.; Müller, R. "Possibility of Bacterial Recruitment of Plant Genes Associated with the Biosynthesis of Secondary Metabolites" *Plant Physiol.* **2003**, *132*, 1153.

⁴⁶ Linder, J.; Blake, A. J.; Moody, C. J. "Total synthesis of siphonazole and its O-methyl derivative, structurally unusual bis-oxazole natural products" *Org. Biomol. Chem.* **2008**, *6*, 3908.

⁴⁷ Zhang, J.; Polishchuk, E. A.; Chen, J.; Ciufolini, M. A. "Development of an Oxazole Conjunctive Reagent and Application to the Total Synthesis of Siphonazoles" *J. Org. Chem.* **2009**, *74*, 9140.

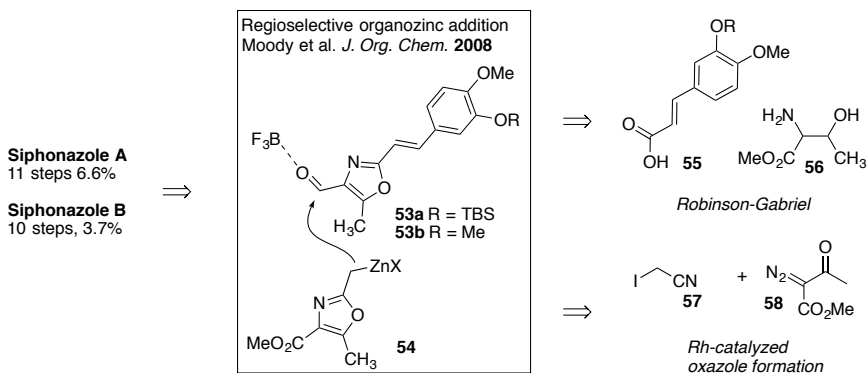
⁴⁸ Baumann, M.; Baxendale, I. R.; Brasholz, M.; Hayward, J. J.; Ley, S., V.; Nikbin, N. "An Integrated Flow and Batch-Based Approach for the Synthesis of O-Methyl Siphonazole" *Synlett* **2011**, 1375.

syntheses, followed by a formal synthesis by Itami.⁴⁹ Enabled by synthetic studies, biological evaluations have revealed moderately potent cytostatic, and antiplasmodial effects – yet their biological effects remain relatively under investigated.

The intriguing structure and interesting biological effects led us to devise a new synthetic route based on our previous findings in oxazole chemistry.

3.1.1. Prior art in the synthesis of the siphonzoles

In the first total synthesis, shown in Scheme 12, Moody *et al.* utilized some classic methodology to construct the oxazole cores. One of the fragments was accessed through a Robinson-Gabriel type cyclization of an amido-keto-ester sourced through a catalytic amide insertion into a rhodium carbene. The other fragment also originates from a diazo-ketone via a Helquist's rhodium catalyzed heterocycladdition. Attempts to utilize an aldol-type strategy for construction of the tethering bond were unsuccessful, proving earlier observations that metalation of 4-carboxyl oxazoles occurs directly at or on substituents in the 5-position.⁵⁰ This was solved by constructing a iodo-oxazole which could be regioselectively converted into zinc-nucleophile **54**.

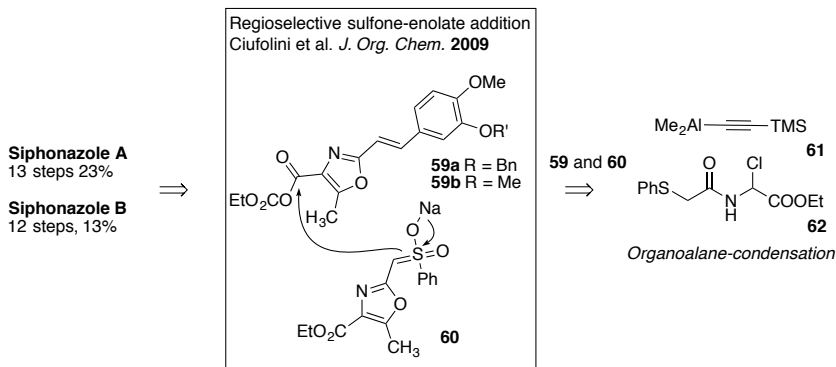


Scheme 12. In the first total synthesis, Moody *et al.* achieved regioselective fragment coupling through the use of an organozinc nucleophile. The synthesis relied on classic methodology for construction of the oxazole cores.

⁴⁹ Meng, L.; Kamada, Y.; Muto, K.; Yamaguchi, J.; Itami, K. "C–H Alkenylation of Azoles with Enols and Esters by Nickel Catalysis" *Angew. Chem. Int. Ed.* **2013**, 10048.

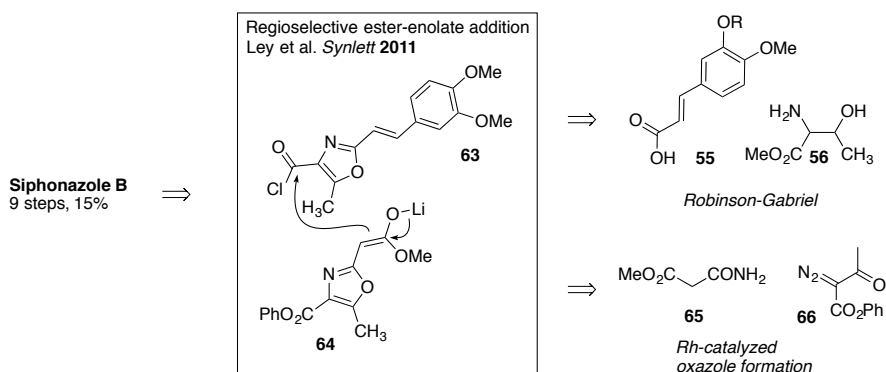
⁵⁰ See reference 47 for a detailed literature overview.

Ciufolini's synthesis involved an unconventional approach for the synthesis of the oxazole cores. A cyclization of an alkynyl-amine to a chloroamide, a method developed in the group, gave oxazole sulfone **60** – a common precursor to both major fragments. Olefination and amalgam mediated sulfone removal gave fragment **59** to which a second molecule of **60** was added through a Claisen-type reaction to form the oxazole-oxazole link.⁴⁷



Scheme 13. Ciufolini used a novel method to construct the oxazole cores, which were both accessed from the same oxazole-sulfone intermediate **60**. The sulfone serves as both a directing group, and as an olefination reagent.

Ley *et al.* developed a partly flow-based synthesis of siphonazole B. Similarly to Ciufolini's solution, an ester was used as a temporary activating group to allow deprotonation in the 2-position of the nucleophilic fragment and promote a Claisen-type reaction to form the tethering bond. The ester was then removed by decarboxylation. Both fragments were accessed through rhodium-catalyzed heterocycladditions, in one case of an amide and in the other case of a nitrile.

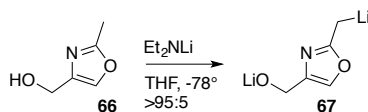


Scheme 14. Ley *et al.* developed a flow-based synthesis of siphonazole B, using an ester as a directing group for the key-bond formation

3.2. Retrosynthesis of siphonazole B

We considered a bond in the C₂-tether of siphonazole B to be most strategic for an initial disconnection in the retrosynthesis. Despite the problems encountered in previous syntheses attempting an aldol-type strategy, we decided to investigate this strategy further.

It was clear that the presence of a 4-carboxyl group in the nucleophilic fragment affected the inherent reactivity of the oxazole, which normally deprotonates on C₂-methyl group. As reviewed by both Moody and Ciufolini,^{46,47} and extensively studied by Cornwall *et al.*,⁵¹ all carboxylic groups in the 4-position of an oxazole tend to direct metalation to the 5-position (or substituents therein). This appeared to be an effect unique to *carboxyl*-oxazoles and, at least in the case of 5-unsubstituted oxazoles, was kinetic and not thermodynamic. As oxazole **66** containing a hydroxymethyl group in the 4-position, was demonstrated to deprotonate in the desired position we hypothesized that the effect originated from coordination to the 4-carboxyl groups.⁵² As this apparent coordination was not mediated by an alkoxide, it should be possible to avoid by simply introducing the carboxylic amide in a later stage of the synthesis.



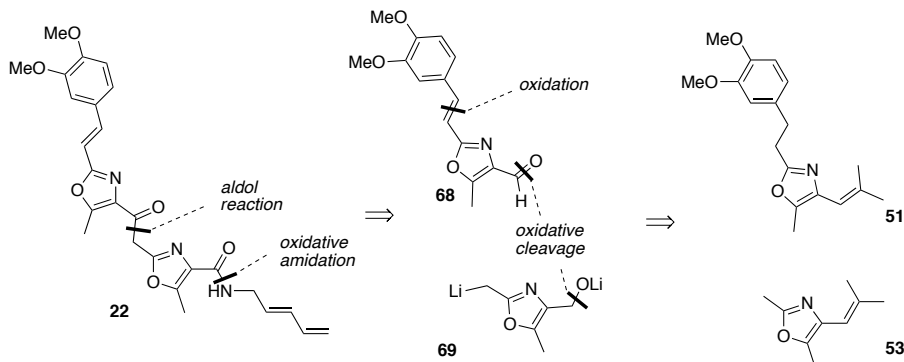
Evans *et al.* *J. Org. Chem.* **1999**

Scheme 15. Evans *et al.* showed that the methyl-group of oxazole **66** was regioselectively lithiated in the presence of lithium-diethylamide.

The two fragments thus obtained would originate from vinyl-oxazoles by oxidative cleavage, and to avoid regioselectivity issues we envisioned introducing the stilbene-unsaturation by oxidation in a later stage.

⁵¹ Cornwall, P.; Dell, C. P.; Knight, D. W. "Regioselectivity in the lithiation of methyl-substituted thiazole- and oxazole-carboxylic acids and carboxamides: general methods for the elaboration of trisubstituted thiazoles and oxazoles" *J. Chem. Soc. Perkin Trans. I* **1991**, 2417.

⁵² Evans, D. A.; Cee, V. J.; Smith, T. E.; Santiago, K. J. "Selective Lithiation of 2-Methyloxazoles. Applications to Pivotal Bond Constructions in the Phorboxazole Nucleus" *Org. Lett.* **1999**, 1, 87.



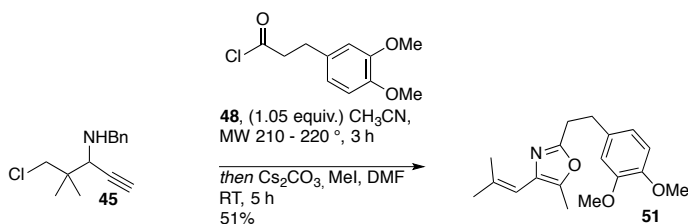
Scheme 16. Our retrosynthetic analysis relies on a regioselective aldol reaction of two fragments obtained by oxidative cleavage of vinyl-oxazoles.

To avoid regioselectivity issues in the oxidative cleavage reaction, we envisioned introduction of the stilbene unsaturation by oxidation. The pentadienyl-amide would be introduced late in the synthesis to avoid side-reactions, and we anticipated using an oxidative amidation protocol for this in order to avoid a lengthy oxidation/activation/amidation sequence.

3.2. The 7-8-9 steps to siphonazole B

3.2.1. Fragment synthesis

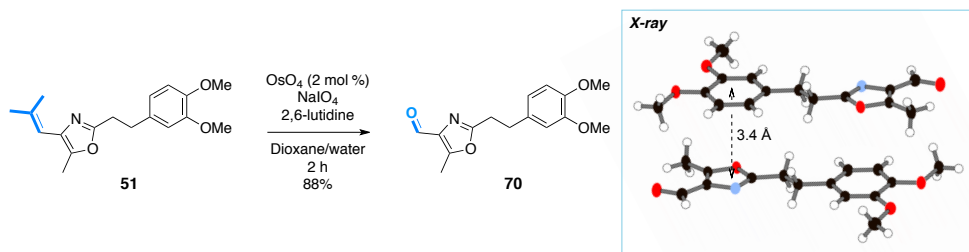
As shown in Table 5 the domino cyclocondensation/1,2-rearrangement was successful for **51**, but despite formation of vinyl oxazole in up to 74% yield, only ca. 30% could be isolated. The remainder of the vinyl-oxazole was lost due to acid-mediated demethylation under the acidic reaction conditions. Attempts to mediate the acidity with various bases such as amines and sodium acetate, and running the reaction at atmospheric pressure to release HCl-gas were unsuccessful. Instead, remethylation with MeI and Cs₂CO₃ in DMF brought the isolated yield of **51** up to 51%. The same yields could be obtained both with and without PPh₃.



Scheme 17. Synthesis of **51** was accompanied by extensive de-methylation. Acceptable yields were obtained after re-methylation with MeI and Cs₂CO₃.

For successful methylation it was crucial to first remove any of the remaining BnCl formed as a side-product in the reaction, as benzylation otherwise occurred. This was done by evaporation from a high-boiling solvent prior to the methylation step – or alternatively, if an excess of PPh₃ was used in the previous step, the majority of BnCl reacted to form the crystalline BnPPh₃Cl, which could be removed by filtration.

Oxidative cleavage of **51** under Lemieux-Johnson conditions smoothly delivered aldehyde **70** as a crystalline solid. The structure was confirmed by scXRD as single-crystals of high quality could be grown by vapor diffusion of hexane into a concentrated solution of **70** in benzene. The structure is shown in Scheme 18.



Scheme 18. Oxidative cleavage of **51** proceeded smoothly to give aldehyde **68**. The scXRD-structure of **68** is shown at the 30% probability level.

The crystals were of high quality (see SI for details on the scXRD) and display an interesting flat sheet-like solid-state structure. The oxazole and benzene rings appear to interact through a parallel-displaced π -stacking, which keeps the layers separated by only 3.4 Å. Other aryl-substituted oxazoles have also been observed to crystallize in a similar manner.⁵³

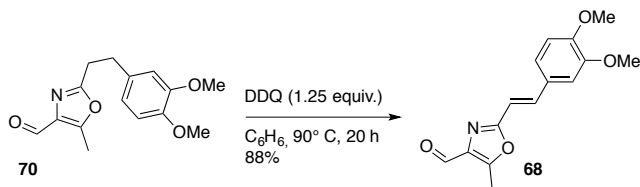
We decided to test two major strategies for the remaining part of the synthesis; to carry through with the fragment coupling using **70** and introduce the stilbene unsaturation in a late-stage oxidation, or to introduce the unsaturation on the comparatively simple bicyclic aldehyde before coupling.

Knowing that oxazoles are incompatible with many inorganic oxidants such as CAN and KMnO₄, the mild yet powerful oxidant DDQ was chosen for the dehydrogenation step. The latter had already been proven compatible with oxazoles for PMB-deprotection⁴⁹ and had been used for synthesis of methoxy-stilbene.⁵⁴ Gratifyingly, DDQ proved effective also in this case and reacted with

⁵³ Hübscher, J.; Felsmann, M.; Seichter, W.; Weber, E. "The *m*-phenylene-bridged bis-oxazole 4,4',5,5'-tetraphenyl-2,2'-*m*-phenylenedi-1,3-oxazole and its bulkily substituted analogue 4,4',5,5'-tetrakis(4-*tert*-butylphenyl)-2,2'-*m*-phenylenedi-1,3-oxazole" *Acta Crystallogr. Sect. C* **2010**, *66*, o623.

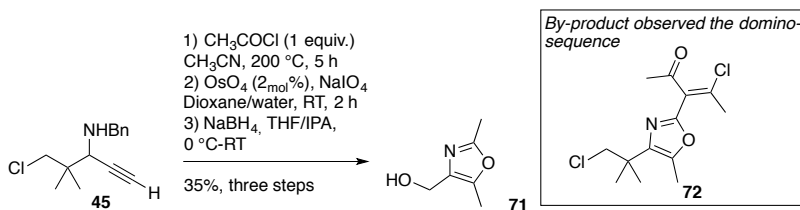
⁵⁴ Findlay, J. W. A.; Turner, A. B. "trans-4-4'-dimethoxystilbene" *Org. Syn.* **1969**, *49*, 53

70 at reflux in dry, oxygen-free benzene to deliver unsaturated aldehyde **68** in 88% yield with >98:2 *E/Z*-ratio.



Scheme 19. DDQ-mediated dehydrogenation to form unsaturated aldehyde **68**.

We then proceeded to investigate the synthesis of the other fragment, alcohol **71**. The optimized conditions proved effective also for this substrate, and additional optimization at this stage proved fruitless with regard to the yield of the desired siphonazole intermediate – but interesting Claisen-type reactivity was observed when large excesses of acetyl chloride was used as the reaction solvent. Chloroenone **72** and similar products were observed originating from an undesired domino cyclocondensation/Claisen/Michael addition-elimination sequence. The reaction and products were not further investigated or characterized, but could provide the basis for new reactions development towards multifunctionalized heterocycles.



Scheme 20. The synthesis of alcohol **71** was performed in three steps without isolation of the volatile intermediates.

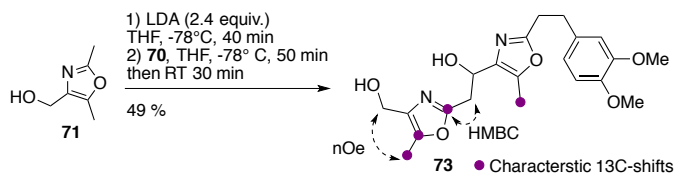
Due to the volatility of vinyl-oxazole **53** and the corresponding aldehyde, the complete synthesis of alcohol **71** was performed without isolation of the intermediates. An aqueous workup and silica-filtration after the domino-rearrangement step was crucial for the oxidative cleavage step to be successful, which otherwise required significantly increased reaction times and catalyst loadings. The presence of triphenylphosphine did not inhibit the osmium catalyst, but its presence complicated purification and led to lower overall yields after reduction – thus the rearrangement cascade was performed without additives. After a simple reductive quench and aqueous workup, the aldehyde reduction was performed in the remaining dioxane after addition of a small amount of

isopropanol and THF. The whole sequence delivered **71** in 35% yield after chromatography allowing us to continue with the synthesis.⁵⁵

3.2.2. Fragment coupling

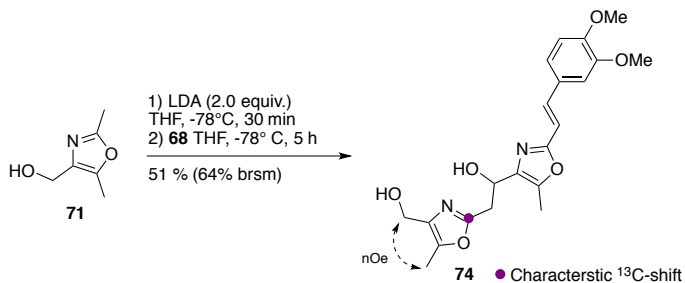
The two oxazole-containing fragments together comprise 80% of the heavy atoms in siphonazole B, and successful coupling of the two would construct the entire core structure, leaving only minor decorations for the rest of the synthesis.

We were pleased to find that the addition of **71** to **70** proceeded with complete regioselectivity for the desired isomer, as proven by 1D and 2D NMR techniques. The diagnostic shifts and correlations used for the structural elucidation are shown in Scheme 21.



Scheme 21. Addition of the dianion of **71** to **70** successfully delivered the desired bis-oxazole skeleton with complete regioselectivity.

A global oxidation at this point was unsuccessful as DDQ only led to extensive decomposition of **73**, and the strategy was abandoned in favor of the early oxidation strategy. The same conditions were applicable also in this case, also here giving complete regioselectivity for the desired isomer.



Scheme 22. Complete regioselectivity was observed also for the aldol reaction with **68**.

⁵⁵ Purification is tedious due to its polarity, water solubility, and fairly high volatility. These properties also provide some unique opportunities – minor impurities can be removed by recrystallization from MTBE or heptane, by sublimation, or by liquid-liquid extraction.

The moderate yield of the reaction was in part due to incomplete conversion, in part due to the basic reaction conditions, which promoted dimerization of the aldehyde fragment. Attempts to run the reaction in different solvents such as MTBE and Et₂O were unsuccessful and occurred with retained yields at best. Similarly, different reaction times and temperatures seemed to have only a marginal effect on the outcome of the reaction – between –80 and –40 °C the reaction proceeded to give similar yields, while it diminished at –20 °C due to extensive by-product formation. The reaction can however be allowed to reach room temperature after the addition is complete without any negative effect on the yield. Attempts to moderate the basicity of the dianion by addition of CeCl₃ or La(OTf)₃ after deprotonation had no significant effect on the yield. NaHMDS was not strong enough to affect formation of the dianion of **71**.

The reaction was routinely conducted on 0.5 g scale to give ca. 300 mg of the desired product.

3.2.3. Oxidative amidation and endgame

Extensive experimentation had to be conducted in order to achieve successful oxidative amidation. Conditions for oxidative amidation involving hypervalent iodine,⁵⁶ transition metals and peroxides,^{57,58,59} quinones,⁶⁰ NCS,⁶¹ transfer hydrogenation,⁶² and sodium chlorite,^{63,64} all led to complete decomposition of the

⁵⁶ Yao, H.; Tang, Y.; Yamamoto, K. "Metal-free oxidative amide formation with *N*-hydroxysuccinimide and hypervalent iodine reagents" *Tet. Lett.* **2012**, 53, 5094.

⁵⁷ Wu, X.-F.; Sharif, M.; Pews-Davtyan, A.; Langer, P.; Ayub, K.; Beller, M. "The First ZnII-Catalyzed Oxidative Amidation of Benzyl Alcohols with Amines under Solvent-Free Conditions" *Eur. J. Org. Chem.* **2013**, 2013, 2783.

⁵⁸ Suto, Y.; Yamagiwa, N.; Torisawa, Y. "Pd-catalyzed oxidative amidation of aldehydes with hydrogen peroxide" *Tet. Lett.* **2008**, 49, 5732.

⁵⁹ Ghosh, S. C.; Ngiam, J. S. Y.; Seayad, A. M.; Tuan, D. T.; Johannes, C. W.; Chen, A. "Tandem oxidative amidation of benzyl alcohols with amine hydrochloride salts catalysed by iron nitrate" *Tet. Lett.* 2013, 54, 4922.

⁶⁰ De Sarkar, S.; Studer, A. "Oxidative Amidation and Azidation of Aldehydes by NHC Catalysis" *Org. Lett.* 2010, 12, 1992.

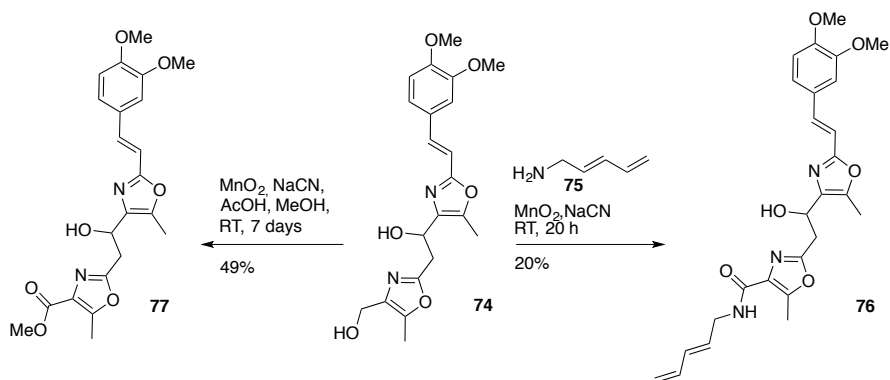
⁶¹ Gaspa, S.; Porcheddu, A.; De Luca, L. "Iron-catalysed oxidative amidation of alcohols with amines" *Org. Biomol. Chem.* **2013**, 11, 3803.

⁶² Ghosh, S. C.; Hong, S. H. "Simple RuCl₃-Catalyzed Amide Synthesis from Alcohols and Amines" *Eur. J. Org. Chem.* **2010**, 2010, 4266.

⁶³ Goh, K. S.; Tan, C.-H. "Metal-free pinick-type oxidative amidation of aldehydes" *RSC Adv.* **2012**, 2, 5536.

starting materials. Several variations of all the conditions were investigated without success.

To investigate the cause and possibly to find a suitable oxidant, we tested various methods for oxidizing primary and secondary alcohols to aldehydes or acids and ketones, respectively, still without success. Activated DMSO, TPAP, and chromium reagents led to low conversion – but aldehyde intermediates could usually be detected briefly only to rapidly decompose.



Scheme 23. Oxidative amidation and esterification of **74** was possible under Corey-Gilman-Ganem conditions.

When MnO_2 was used, however, an aldehyde could be isolated in moderate yield, but further oxidation rapidly led to decomposition. This suggested that the coexistence of the aldehyde and ketone functionalities was causing the problems. This could be attributed to the high nucleophilicity of the enol form of the ketone, which has been observed to participate in side-reactions also by Moody during attempts to methylate siphonazole A.⁴⁶

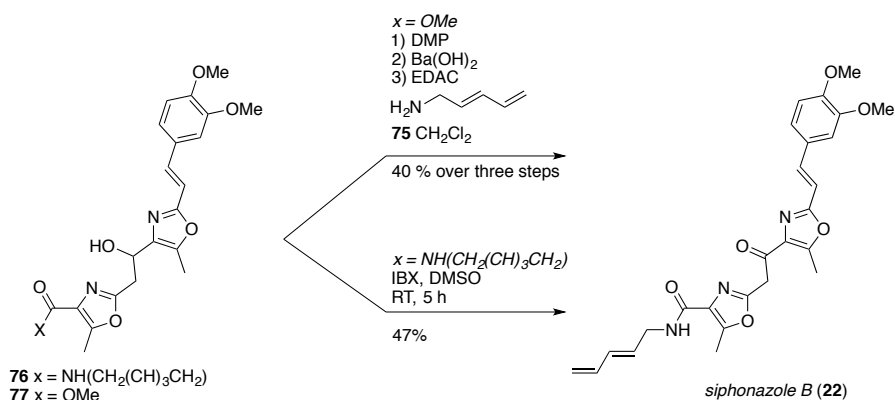
With this knowledge we continued to investigate oxidative amidations that would only affect the primary alcohol to avoid coexistence with the ketone. MnO_2 -mediated Corey-Gilman-Ganem oxidation⁶⁵ was successful and delivered methyl ester **77** in 49% yield – comprising a formal synthesis of siphonazole B.

⁶⁴ Dalcanale, E.; Montanari, F. "Selective oxidation of aldehydes to carboxylic acids with sodium chlorite-hydrogen peroxide" *J. Org. Chem.* **1986**, *51*, 567.

⁶⁵ Corey, E. J.; Gilman, N. W.; Ganem, B. E. "New methods for the oxidation of aldehydes to carboxylic acids and esters" *J. Am. Chem. Soc.* **1968**, *90*, 5616.

A variation of the protocol was also successful in providing the desired hydroxy-amide **76**,⁶⁶ albeit in only 20% yield, which could not be improved despite extensive studies on the reaction time, temperature, stoichiometry, solvent, and cyanide source. It was neither possible to achieve amidation with MnO₂ in the presence of other activators such as NHS, HFIP, or carbene precursors.

Amide **76** lacks only oxidation of the secondary alcohol to be converted to siphonazole B. This was attempted under different conditions without success. Alcohol **76** was completely unreactive to both DMP and a variation of the Swern protocol, including acetylacetone to avoid side reactions of the easily enolizable ketone.⁶⁷ PDC led to extensive by-product formation. Only IBX in DMSO successfully oxidized **76** to siphonazole B in 48% yield, the remainder of the material was converted into a hydroxy-ketone by-product.



Scheme 24. Oxidation of hydroxy-amide **76** by IBX delivered siphonazole B in 47% yield. A three-step protocol could also be used to convert ester **77** into siphonazole B, as previously reported by Moody *et al.*

We successfully also converted **76**, an intermediate in Moody's synthesis of siphonazole B, into the final compound using a variation of the published method.

⁶⁶ Foot, J. S.; Kanno, H.; Giblin, G. M. P.; Taylor, R. J. K. "Esters and Amides from Activated Alcohols using Manganese(IV) Dioxide: Tandem Oxidation Processes" *Synthesis* **2003**, 2003, 1055.

⁶⁷ For a variation of the Swern-protocol suitable for oxidation to highly reactive enolizable ketones see: Williams, D. R.; Kiryanov, A. A.; Emde, U.; Clark, M. P.; Berliner, M. A.; Reeves, J. T. "Studies of stereocontrolled allylation reactions for the total synthesis of phorbazole A" *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 101, 12058.

3.3. Conclusions

In conclusion, we have developed a concise synthesis of siphonazole B from a commercially available chloroaldehyde in 9-steps (7 synthetic operations). The synthesis was enabled by a new domino cyclocondensation/1,2-oxazole rearrangement reaction that delivers 4-vinyl oxazoles in a single step from acyclic precursors. Known regioselectivity issues in the key step were solved in a novel simple way by introducing the siphonazoles' unprecedented pentadienyl amide in a late stage of the synthesis by oxidative amidation. This also constitutes the first example of a direct oxidation of a (4-oxazolyl)-methanol to the carboxylic acid stage.

4. Iridium-catalyzed skeletal rearrangement

4.1. Introduction

Iridium's potential to act as a catalyst has long been neglected in the literature, but since Crabtree's report⁶⁸ on the unusually powerful hydrogenation catalyst [Ir(cod)PyPCy₃]PF₆, its importance in organic chemical transformations has skyrocketed. Its use now spans many fields within organic chemistry, often promoting green and atom efficient processes. Applications span from alkylations and cycloadditions,⁶⁹ to CO₂ activation,⁷⁰ oxidations,⁷¹ and carbenoid group transfer reactions,⁷² among many others.

We have an ongoing research program directed towards development of new transition metal catalyzed reactions and within this developed the first iridium-catalyzed 5+2 cycloaddition between alkynes and vinylcyclopropanes.⁷³ Within this work, we investigated the mechanism of the reaction computationally. The calculations suggested, as shown in Scheme 25, that the iridacyclooctadiene intermediate **3_{Ir}** in the iridium catalyzed reaction was significantly more stable than the corresponding known rhodium species – as expected when going from

⁶⁸ Crabtree, R. H.; Felkin, H.; Morris, G. E. *J. Organomet. Chem.* **1977**, *141*, 205.

⁶⁹ Takeuchi, R.; Kezuka, S. "Iridium-Catalyzed Formation of Carbon-Carbon and Carbon-Heteroatom Bonds" *Synthesis* **2006**, 2006, 3349.

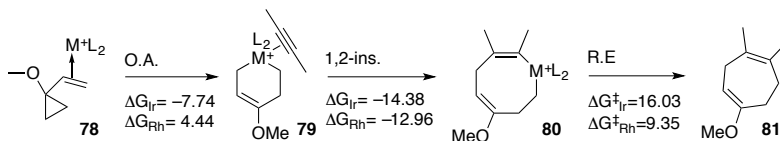
⁷⁰ Fernández-Alvarez, F. J.; Iglesias, M.; Oro, L. A.; Polo, V. "CO₂ Activation and Catalysis Driven by Iridium Complexes" *ChemCatChem* **2013**, *5*, 3481.

⁷¹ Suzuki, T. "Organic Synthesis Involving Iridium-Catalyzed Oxidation" *Chem. Rev.* **2011**, *111*, 1825.

⁷² Schafer, A. G.; Blakey, S. B. "Ir-Catalyzed enantioselective group transfer reactions" *Chemical Society Reviews* **2015**, *44*, 5969.

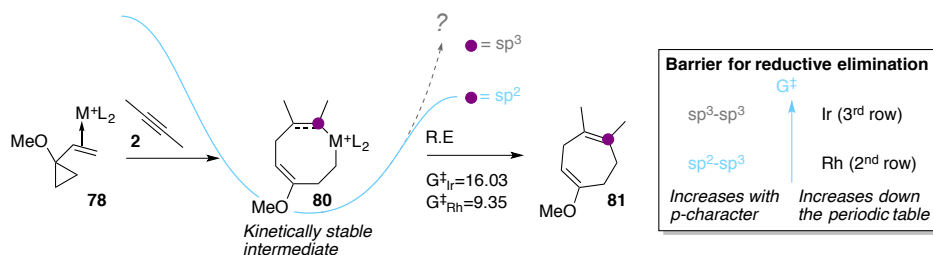
⁷³ Melcher, M.; von Wachenfeldt, H.; Sundin, A.; Strand, D. "Iridium Catalyzed Carbocyclizations: Efficient (5+2) Cycloadditions of Vinylcyclopropanes and Alkynes" *Chem. Eur. J.* **2015**, *21*, 531.

rhodium to iridium.⁷⁴ This increase in stability led to a higher barrier for reductive elimination as compared to rhodium, making it the rate-determining step in our case.⁷³



Scheme 25. The iridacycle **80_{Ir}** lies deep in an energy well, making reductive elimination the rate-determining step.

We envisioned that by further stabilizing this intermediate by conversion of the Ir-C(sp²)-bond to an Ir-C(sp³) bond in this intermediate, the reductive elimination leading to 5+2 products could effectively be shut down in favor of other pathways due to the higher energetic barrier for sp³-sp³-reductive elimination.^{75,74}



Scheme 26. We anticipate the reductive-elimination barrier for a completely sp³-bound iridacyclooctene to be even higher than that for **80**.

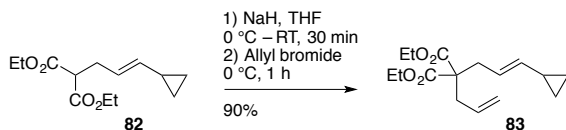
⁷⁴ Frenking, G.; Deubel, D. V. *Theoretical aspects of transition metal catalysis* Berlin; New York: Springer, 2005.

⁷⁵ Wang, Y.; Wang, J.; Su, J.; Huang, F.; Jiao, L.; Liang, Y.; Yang, D.; Zhang, S.; Wender, P. A.; Yu, Z.-X. "A Computationally Designed Rh(I)-Catalyzed Two-Component [5+2+1] Cycloaddition of Ene-vinylcyclopropanes and CO for the Synthesis of Cyclooctenones" *J. Am. Chem. Soc.* **2007**, *129*, 10060.

4.2. Development of the skeletal rearrangement reaction

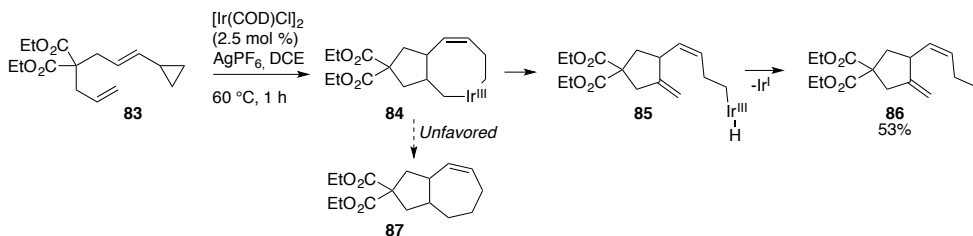
4.2.1. Proof for the hypothesis of an alternative pathway

To test our hypothesis, we set out to synthesize VCP-ene **83**. Starting from cyclopropylallyl-malonate **82**, available in three steps from cyclopropanecarbaldehyde according to the method of Murai *et al.*,⁷⁶ we synthesized alkene-tethered vinyl cyclopropane (VCP-ene) **83** by simple alkylation.



Scheme 27. Alkylation of known VCP **82** delivered VCP-ene **83** for further studies of our hypothesis.

We initially tested the hypothesis by simply subjecting VCP-ene **83** to a catalytic amount of $[\text{Ir}(\text{cod})\text{Cl}]_2$ and AgPF_6 at 60 °C in DCE. The starting material was indeed completely converted within one hour and isolation of the products revealed **86** to be the major constituent at 53 % yield.



Scheme 28. The VCP-ene **83** did indeed react to give a product distinct from that of the corresponding [5+2] reaction.

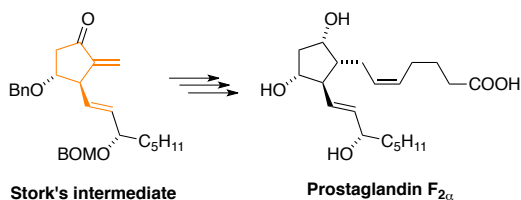
86 presumably arises through a mechanism initially similar to the iridium-catalyzed [5+2] cycloaddition wherein the iridium complexes to **83** then undergoes oxidative addition to form an iridacyclohexene intermediate. 1,2-insertion into the alkene would then lead to the kinetically stabilized sp^3 - sp^3 bonded iridacyclooctene **84**. As predicted, reductive elimination to the seven-membered ring was prohibited and the reaction hereafter took an alternative path – the major

⁷⁶ Chatani, N.; Inoue, H.; Morimoto, T.; Muto, T.; Murai, S. "Iridium(I)-Catalyzed Cycloisomerization of Enynes" *J. Org. Chem.* **2001**, *66*, 4433.

being ring-opening by β -hydride elimination leading to primary alkyliridium-hydride **85** which presumably rapidly undergoes reductive elimination to regenerate the catalyst and form the product **86**.

The reaction is complementary to that of rhodium-catalysis, which catalyzes the [5+2] cycloaddition of VCP-enes and constitutes the first example of such reactivity for iridium. Although similar reactivity has reportedly been observed as a side reaction in the rhodium-catalyzed [5+2] cycloaddition with sterically congested substrates,⁷⁷ it has, to the best of our knowledge, never been exploited synthetically.

The product is an allyl-alkylidene cyclopentane which is structurally reminiscent of the prostaglandin-core structure, and in fact constitutes the core structure of Stork's intermediate used in the synthesis of PGF_{2 α} ,⁷⁸ and has been the target of several formal syntheses.^{79,80}



Scheme 29. Stork's intermediate, with the vinyl-methylene-cyclopentane core highlighted in orange, was used in the synthesis of PGF_{2 α}

⁷⁷ Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A. "First Studies of the Transition Metal-Catalyzed [5+2] Cycloadditions of Alkenes and Vinylcyclopropanes: Scope and Stereochemistry" *J. Am. Chem. Soc.* **1998**, *120*, 1940.

⁷⁸ Stork, G.; Isobe, M. "General approach to prostaglandins via methylenecyclopentanones. Total synthesis of (+)-prostaglandin F_{2.α}" *J. Am. Chem. Soc.* **1975**, *97*, 4745.

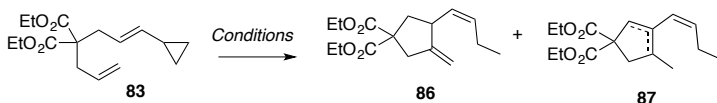
⁷⁹ Togashi, K.; Terakado, M.; Miyazawa, M.; Yamamoto, K.; Takahashi, T. "Chirality transfer in the palladium(0)-catalyzed cyclization of 3-oxo-8,9-dihydroxytetradeca-1,6-diene derivatives into 2-methylenecyclopentanones" *Tet. Lett.* **1994**, *35*, 3333.

⁸⁰ Nakazawa, M.; Sakamoto, Y.; Takahashi, T.; Tomooka, K.; Ishikawa, K.; Nakai, T. "A new approach to asymmetric synthesis of Stork's prostaglandin intermediate" *Tet. Lett.* **1993**, *34*, 5923.

4.2.2. Ir(cod) and other catalytic systems catalyze the reaction

We decided to study this interesting and potentially useful reaction further. At the outset we studied the catalytic potential of *in situ* generated cationic iridium species formed by the addition of a silver salt to [Ir(cod)Cl]₂ and [Ir(dbcot)Cl]₂. Up to 66% yield was achievable with both Ir(cod)PF₆ and Ir(dbcot)PF₆, but the latter required a higher temperature to reach full conversion. Preformed cationic Ir(cod)-species stabilized by CH₃CN, PhCN, or toluene all required higher catalyst loadings, temperature, or reaction times to reach full conversion with decreased yields. Similarly, commercially available Ir(cod)₂BARf promoted the reaction under slightly more forcing conditions with reduced yields due to formation of by-product **87**.

Table 7. Initial screening of catalysts for the skeletal rearrangement process.



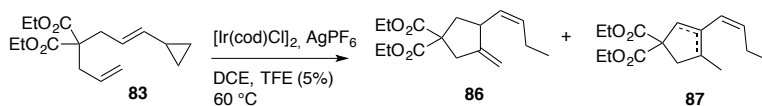
The reaction scheme shows substrate **83**, which is a cyclopropane ring substituted with two ethyl ester groups and a vinyl group, reacting under conditions to form two products: **86** (a rearranged cyclopropane with a vinyl group and two ethyl ester groups) and **87** (a rearranged cyclopropane with a vinyl group and two ethyl ester groups, but with a different ring substitution pattern).

| Catalyst (mol%) | Additive ^b | T /°C | t | Yield 86 /% ^c | Yield 87 /% |
|--|-----------------------|-----------|---------------|---------------------------------|--------------------|
| Ir(cod)PF₆ (5)^a | - | 60 | 45 min | 66 | 6 |
| Ir(dbcot) PF ₆ (5) ^a | - | 75 | 40 min | 66 | nd |
| Ir(cod)PF ₆ (2.5) ^a | - | 60 | 1.5 h | 66 | nd |
| Ir(cod) ₂ BARf (1.25) | - | 75 | 18 h | 60 | 11 |
| Ir(cod)(toluene)PF ₆ (2.5) | TFE ^b | 75 | 6 h | 54 | 7 |
| Ir(cod)(PhCN) ₂ PF ₆ (5) | - | 75 | 2 h | 54 | trace |
| Ir(dbcot)PF ₆ (2.5) ^a | - | 100 | 3 h | 53 | 3 |
| Ir(cod)(CH ₃ CN) ₂ PF ₆ (2.5) | - | 100 | 1.5 h | 52 | nd |
| Ir(cod) ₂ BARf (2.5) | TFE ^b | 85 | 25 min | 55 [95] | 11 |
| Ir(cod) ₂ BARf (2.5) | - | 75 | 1 h | 58 [87] | 8 |
| Ir(cod)(toluene)PF ₆ (2.5) | - | 75 | 20 h | 40 [90] | 8 |

Reactions were performed by adding substrate **83** (25 mg, 89 μmol) to a solution of the catalyst (appropriate amount) in DCE (0.25 ml). Yields were measured by NMR using mesitylene as an internal standard employing a 20 s relaxation delay. ^a Catalysts were generated *in situ* by addition of AgPF₆ (1.0 equiv.) to the appropriate iridium-chloride precursor in DCE. ^b Added to as an additional 5% vol. to the solvent. ^c Numbers in brackets signify conversion, which was measured by NMR as described for yield.

The loading of Ir(cod)PF₆ could be reduced to 2.5% (1.25% [Ir(cod)Cl]₂) with retained yields. Further reduction led to longer reaction time and reduced yield, and the reactivity was completely shut down at 1_{mol}% Ir(I) as shown in Table 8.

Table 8. Reduced Ir(cod)⁺ loadings are acceptable down to 2.5%.

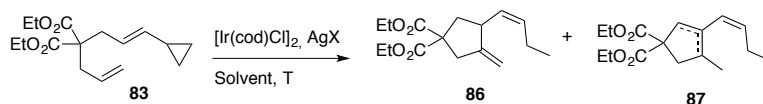


| Ir(I) loading (mol%) | t | Yield 2 /% | Yield 3 /% |
|----------------------|---------------|-------------------|-------------------|
| 5 | 25 min | 62 | ~5 |
| 5 | 50 min | 53 | 21 |
| 3.5 | 20 min | 67 | 9 |
| 3 | 1.5 h | 66 | n.d. |
| 2.5 | 1.5 h | 66 | n.d. |
| 1.5 | 4.5 h | 57 | n.d. |
| 1 | > 24 h | n.d. | n.d. |

Reactions were performed as described in Table 7.

The optimum catalyst loading with respect to both reaction time and yield appeared to be 3.5% Ir(I), which was used in further studies. In attempts to further improve the reaction yield, we studied the effect of the solvent and counterion as shown in Table 9. The reaction did proceed to full conversion in THF but with somewhat reduced yields. In toluene and dioxane however, no product could be detected even after 24 h at 60 °C. This can presumably be attributed to the low solubility of the cationic iridium species in these solvents. Isopropanol was tolerated in the reaction albeit with severely reduced yield and increased reaction time to full conversion. Addition of 2,2,2-trifluoroethanol led to increased yields at higher concentrations, but could only be added up to 80% by volume to retain solubility of the catalyst precursors. In 80% TFE/DCE, the reaction could be run at room temperature to give 72% **86** within 21 h.

Table 9. Higher concentrations of TFE enable milder reaction conditions and higher yields.



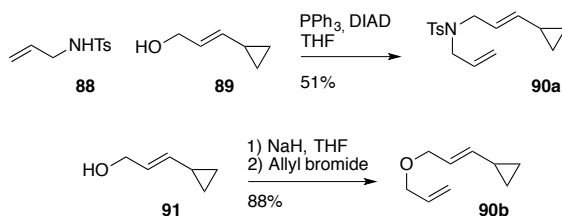
| Dimer (mol%) | Counterion | Solvent | T / °C | t | Yield 2 / % | Yield 3 / % |
|--------------|------------------|----------------|--------|--------|-------------|-------------|
| 1.7 | SbF ₆ | TFE/DCE 80:20 | RT | 21 h | 72 | 7 |
| 1.7 | SbF ₆ | TFE/DCE 80:20 | 50 | 30 min | 69 | 6 |
| 1.7 | SbF ₆ | TFE/DCE 40:60 | RT | 21 h | 67 | 13 |
| 1.7 | SbF ₆ | HFIP/DCE 80:20 | RT | 9 h | 58 | 16 |
| 1.75 | PF ₆ | THF | 60 | 1 h | 53 | n.d. |
| 2.0 | PF ₆ | THF | 60 | 1 h | 50 | n.d. |
| 1.7 | SbF ₆ | IPA/DCE 85:15 | 60 | 3 d | 29 | 19 |
| 2.5 | PF ₆ | Toluene | 60 | > 24 h | n.d. | n.d. |
| 2.5 | PF ₆ | Dioxane | 60 | > 24 h | n.d. | n.d. |
| 1.7 | SbF ₆ | MeOH/DCE 85:15 | 60-75 | > 3 d | n.d. | n.d. |

Reactions were performed as described in Table 7.

Isolation of **86** by flash chromatography generally leads to around 30% more mass than expected from the NMR-quantification, despite only minor impurities being observed after purification and quantitative NMR-conditions. After chromatography, the same NMR-quantification method only underestimates the yield by approximately 7%. There is clearly a discrepancy between isolated and measured yields that have to be investigated further.

4.2.3. Heteroatom-tethered VCP-enes are tolerated to a lesser extent

Using pre-optimized conditions we tested some other substrates in the reaction. Tosylamide **90a** and ether **90b** – synthesized as shown in Scheme 30 both delivered the desired reorganized products in short reaction times as shown in Table 10. Amide **91a** was isolated in 48% yield, with approximately 10% of the by-product **92a**. The latter appear to have formed by migration of the *exo*-double bond in the initial product **91a**, but the isomeric *endo* 1,3-diene could be observed.

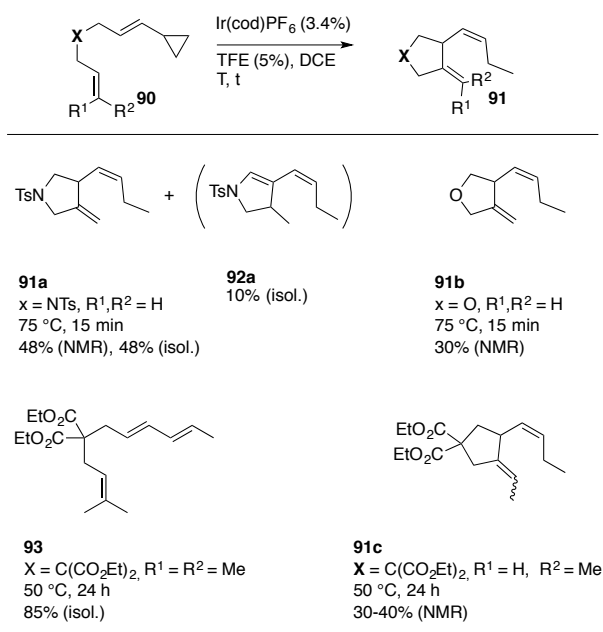


Scheme 30. Synthesis of heteroatom-tethered VCP-ene substrates **90a-b**.

The fairly low yield of **91b** is presumably related to side-reactions due to cleavage of the bis-allylic ether. Due to its volatility, it could not be isolated by chromatography but instead quantified solely by NMR.

The reaction appears to be sensitive to steric hindrance at the alkene moiety. With an *E*-methyl substituted alkene low yields of 30-40% were observed by NMR, and with a 1,1-dimethyl alkene the reactivity was completely shut down in favor of VCP-ring opening to produce **93**. The latter reaction presumably occurs through formation of an iridacyclohexene, which instead of inserting into the pendant alkene undergoes β -elimination followed by reductive elimination.

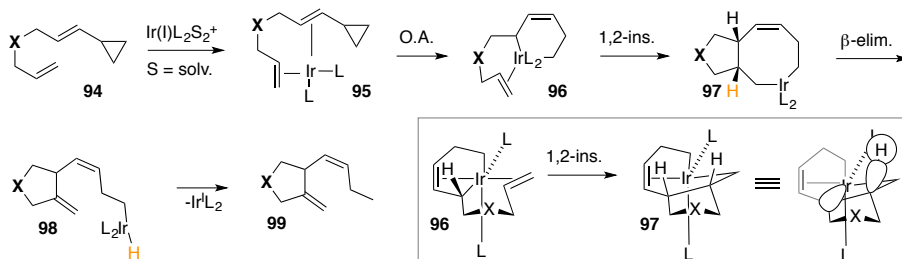
Table 10. Additional substrates in the skeletal rearrangement reaction.



4.2.4. Labeling experiments corroborate the mechanistic hypothesis

As stated in section 4.2.1. we hypothesized that the mechanism for the skeletal rearrangement reaction would start out initially similar to the [5+2] cycloaddition we have previously disclosed.⁷³ As shown in Scheme 31 the reaction is initiated when iridium coordinates to the VCP-ene, which is followed by oxidative addition to form iridacyclohexene **96**. This then undergoes 1,2-insertion to the pendant

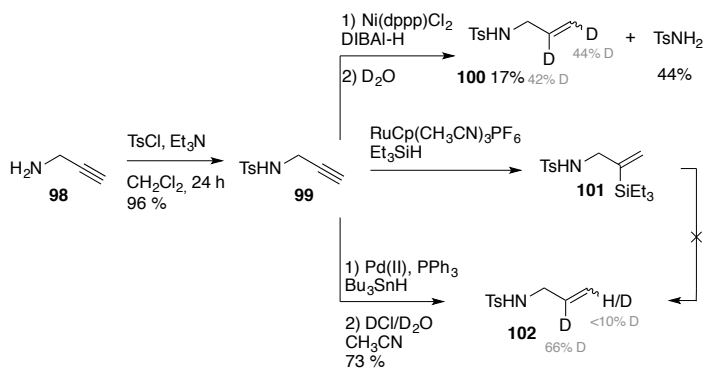
alkene to form the eight-membered iridacycle **97**. Due to the increased barrier for reductive elimination of this bis-(sp³)-alkyliridium compound, it instead undergoes a ring-flip type reorganization to allow β-elimination to hydrido-iridium-alkyl compound **98** – which then undergoes reductive elimination to generate the



product and regenerate the catalyst.

Scheme 31. Our proposed mechanism for the skeletal rearrangement process. The initial conformation of iridacycle **97** is proposed in the square inset, which demonstrates the unfavourable orbital overlap between Ir and the hydrogen atom highlighted in orange. A major conformational change is required to enable the β-elimination step.

We anticipated that diagnostic deuterium-labeling experiments would be suitable to prove these last two steps. Thus, due to the relative ease to work with allyl-tosylamide as compared to e.g. allyl-bromide, we set out to synthesize a deuterium-labeled variant of **90a**.



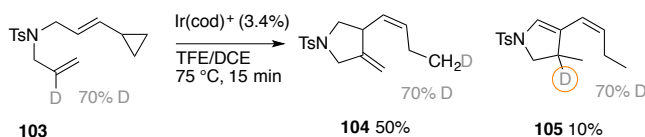
Scheme 32. Some of the routes investigated towards deuterium-labeled allul-tosylamide **102**. Only the hydrostannylation/deutero-desannylation route was successful.

As shown in Scheme **32** we initially tested the nickel-catalyzed internal hydroalumination of alkyne **99**, but the reaction unfortunately didn't provide any regioselectivity. Ruthenium-catalyzed hydrosilylation occurred with complete internal regioselectivity, but the TES-group was resistant to deutero-desilylation even under forcing conditions (KF, TBAF, AgF, DCl/D₂O). Lastly, palladium-

catalyzed hydrostannylation proceeded with good selectivity for the internal position, and was readily destannylated in DCl/D₂O to give the desired compound **102** with approximately 70% isotopic purity. It was then converted to **103** by the same method as used previously.

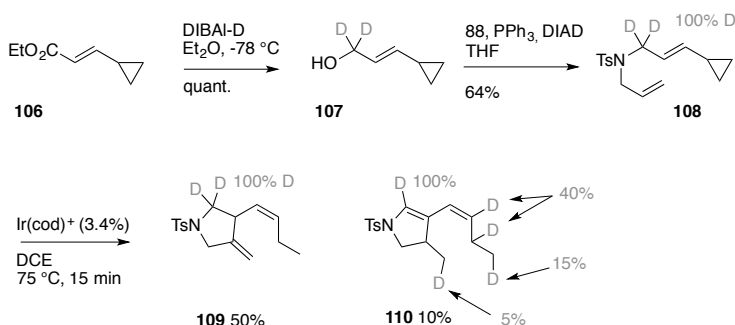
As expected, **103** underwent the skeletal rearrangement to give **104** with the deuterium label moved to the terminal methyl group on the side-chain as shown in Scheme 33, which proves our hypothesis of a β -elimination/reductive elimination pathway.

Remarkably, however, the by-product **105** that we hypothesized would be formed by double-bond migration, still had the deuterium label in its initial position. This suggests that an alternative pathway, completely distinct to that leading to **104**, is operational in its formation. We anticipated an allyliridium species to be involved and set out to synthesize another diagnostically labeled compound.



Scheme 33. Labeled VCP-ene **103** underwent the expected reaction to give **104**, wherein the deuterium label has migrated to the end of the alkyl chain. Byproduct **105** is remarkable however, as the untouched deuterium label suggests a completely distinct reaction pathway.

As shown in Scheme 34, deuterium-labeled amide-tethered VCP-ene was synthesized by a Mitsunobu-reaction of labeled alcohol **107**. The latter was made by DIBAL-D mediated reduction of known ester **106**.



Scheme 34. Labeling of the allylic position on the VCP-part of the molecule led to a complex labeling pattern in by-product **110**.

As expected, the major product of the skeletal rearrangement with **106** as the substrate is **109**, with the deuterium-labeled position completely intact and

untouched. The by-product **110** however has a much more complex pattern of deuterium atoms, which does not point to a specific, or at least readily conceivable, pathway.

4.3. Conclusions

The research presented in chapter 4 started out with the hypothesis that we would be able to access reactivity unprecedented for iridium by making small changes to an intermediate involved in another reaction we developed. Due to the already high energetic barrier iridacyclooctadienes have to cross in the Ir-catalyzed [5+2] cycloaddition of VCP's and alkynes, we anticipated that a hybridization change that would increase this barrier further could lead us to new reaction pathways.

Indeed, by using VCP-enes instead of VCP-yne, we discovered a new reaction leading to compounds distinct to those available by e.g. rhodium-catalysis. We optimized this reaction with respect to the catalyst, solvent and temperature and were thus able to access densely functionalized five-membered carbo- and heterocycles in good to moderate yields.

We studied the reaction mechanism and acquired proof for a major, probable pathway. We also discovered that another pathway – not yet elucidated, was occurring simultaneously.

The project requires further work in optimization and substrate scope, as well as mechanistic studies, but also provides a ground for further development on iridium-catalyzed higher-order cycloadditions.

5. Conclusions

This thesis deals with expanding the organic chemists' toolbox by the development of new complexity generating reactions – but it also deals with improving our understanding of unknown but potentially useful processes.

For example, Chapter 2 deals with the development of a domino-1,2-rearrangement reaction for rapid access to valuable 4-vinyl oxazoles. We developed the reaction and studied one of the constituent steps in more detail, which revealed an interesting reaction mechanism relying on unprecedented anchimeric assistance by oxazole. This is interesting in its own right, but it also illustrates together with the next chapter how relatively unexplored the chemistry of oxazoles and heterocycles in general is – or rather how much more there is to learn and explore.

The next chapter, 3, entails the development of a concise total synthesis of the cytostatic and antiplasmodial natural product siphonazole B. This short reaction sequence was enabled by the rapid construction of vinyl oxazoles using the methodology developed in the previous chapter. Oxidative cleavage of these intermediates lead to two key fragments containing 80% of the target core structure, from a single acyclic precursor in only three synthetic operations. The coupling of these fragments demonstrates a simple and atom efficient solution to a known regioselectivity issue – we reach complete regioselectivity by simply introducing the cause of the problem in a later stage. But also in this chapter, we observe some areas that would benefit from further development – in particular the lack of known tandem oxidation processes that tolerate complex and sensitive molecules.

The last chapter demonstrates how we can learn from observations that initially appear less significant. We show how the knowledge about a shift in rate-determining step when changing metals can spark ideas that lead to completely new discoveries. This is why *all* and *any* new knowledge about chemical reactivity is important!

6. Perspectives and future work

We hope the work presented herein will be received and understood from its full potential – the reaction entailed in chapter 2 enables access to valuable 4-vinyl oxazoles, a structure hitherto selectively available only through lengthy synthetic sequences and in scattered reports on direct methods. Its value should have been well showcased by its use to access both fragments in our total synthesis of siphonazole B discussed in chapter 3. In this chapter we also demonstrate valuable methods for direct access to 4-carboxylic oxazole esters and amides in the context of a complex and sensitive natural product – important early results that suggest a need for further development and improvement of such reactions. There are several more areas within this work that require further work and development. In particular, further computational studies on the reaction mechanism of the 1,2-oxazole rearrangement reaction are needed in order to explain the complete reaction. Such computations are underway and will be reported in due course.

The last chapter demonstrates a completely new reaction pathway for iridium catalysis. The development of the skeletal rearrangement reaction gives access to complex structures in a rapid manner, while more studies are required to demonstrate its generality. The reaction was enabled by the kinetic stability of a iridacycle intermediate – which could possibly be exploited for further development of new reactions. For example, insertion of π -components such as CO or alkynes into the presumably long-lived iridacyclooctane could open up possibilities to develop higher order cycloadditions such as [5+2+1] or [5+2+2] which would give access to eight, and nine-membered rings, respectively.

To conclude – we have answered many questions in this work, but many more have emerged for us and anyone to answer and explore further.