

**APPLICATION OF IMINIUM ACTIVATION TECHNOLOGIES TO
NATURAL PRODUCT SYNTHESIS:
Total Syntheses of the Spiculisporic Acids,
Progress Towards the Total Synthesis of Cylindrocyclophane F,
and Formal Synthesis of Cylindrocyclophane A.**

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ABSTRACT

The first enantioselective, catalytic vinylogous Mukaiyama-Michael reaction of siloxyfurans with simple α,β -unsaturated aldehydes has been reported using chiral imidazolidinones. This methodology provides access to enantioenriched β -butenolides, a privileged motif in organic synthesis. The utility of this organocatalytic Mukaiyama-Michael reaction was highlighted by the total syntheses of $(-)$ -spiculisporic acid and $(-)$ -5-*epi*-spiculisporic acid.

Investigations into the total syntheses of cylindrocyclophanes A and F necessitated the development of a novel *B*-alkyl Suzuki cross-coupling of trimethylanilinium salts using a nickel(0) catalyst and bulky phosphine ligand. This methodology study revealed a very competitive nickel-catalyzed demethylation pathway, which produced dimethylaniline byproducts. A possible explanation for this side reaction is discussed. This technology was applied to a dimerization strategy for the C_2 -symmetric cylindrocyclophane F. Synthesis of a dimerization precursor included an enantioselective organocatalytic 1,4-addition of 3,5-dimethoxy-*N,N*-dimethylaniline into an α,β -unsaturated aldehyde. However, the *B*-alkyl Suzuki cross-coupling was unsuccessful in promoting a dimerization.

Next, the synthesis of cylindrocyclophane A was explored using an alternative ring-closing metathesis dimerization strategy. A dimerization precursor was to be assembled via the cross-coupling of trimethylanilinium salts with potassium (vinyl)trifluoroborate salts, whose syntheses featured an organocatalytic 1,4-conjugate reduction of a α,β -disubstituted enal. This cross-coupling strategy revealed olefin isomerization as a major

side-reaction in the nickel-catalyzed Suzuki dimerization, making this route a non-productive approach to the natural product.

Lastly, formal synthesis of cylindrocyclophane A was accomplished using (i) a nickel-catalyzed Stille cross-coupling of an activated vinyl stannane with a judiciously chosen trimethylanilinium salt and (ii) an asymmetric palladium-catalyzed allylic alkylation of an acyclic ketone. The latter represents the first example of application of the $\text{Pd}_2(\text{dba})_3/t\text{-Bu-PHOX}$ catalyst system to effect an asymmetric allylic alkylation on an acyclic system with good stereoselectivity. This route constituted a formal synthesis of cylindrocyclophane A in eight linear steps, making it more efficient than the published route to the same advanced intermediate reported by Smith, which was synthesized in eleven steps.

Table of Contents

Acknowledgements.....	iv
Abstract.....	vi
Table of Contents.....	viii
List of Schemes	xii
List of Figures.....	xiv
List of Tables.....	xviii
List of Abbreviations.....	xx

Chapter 1: Enantioselective LUMO-Lowering Organocatalysis.

I. Introduction.....	1
II. A General Approach to Enantioselective LUMO-lowering catalysis	5
i. Chiral imidazolidinones as privileged organocatalysts.....	6
III. Summary of Thesis Research	10

Chapter 2: Total Syntheses of the Spiculisporic Acids: Exploitation of the Organocatalytic Vinylogous Mukaiyama-Michael Addition.

I. Introduction.....	11
i. \square -Butanolide architecture	11
ii. The Mukaiyama-Michael reaction	15
iii. Mukaiyama-Aldol versus Mukaiyama-Michael addition.....	16
II. Organocatalytic Vinylogous Mukaiyama-Michael Reaction.....	18
i. Initial investigations.....	19

ii. Scope of the organocatalytic Mukaiyama-Michael reaction	21
III. Total Syntheses of the Spiculisporic Acids.....	23
i. Background.....	23
ii. Investigation of key organocatalytic Mukaiyama-Michael reaction.....	25
iii. Completion of 5- <i>epi</i> -spiculisporic acid.....	30
iv. Reassessment of the organocatalytic step	32
v. Completion of spiculisporic acid.....	34
IV. Proposed Explanation for the Change in Diastereoselectivity	35
i. Approach of the nucleophile onto the iminium system	36
ii. Mukaiyama-Michael into methyl-4-oxobutenoate	37
iii. Mukaiyama-Michael into <i>tert</i> -butyl-4-oxobutenoate	39
iv. Mukaiyama-Michael into crotonaldehyde	40
v. Another transition state consideration	42
Conclusion	43
Supporting Information.....	44

Chapter 3: Progress Towards the Total Synthesis of Cylindrocyclophane F: Investigations into a Novel B-alkyl Suzuki Cross-Coupling.

I. Introduction to the Cylindrocyclophanes.....	43
i. Isolation and structure determination	53
ii. Proposed biosynthesis of the cylindrocyclophanes.....	55
II. Previous Synthetic Efforts to the Cylindrocyclophanes.....	57
i. Albizati's approach to a cylindrocyclophane model	57
ii. Trost's approach to cylindrocyclophane A	61
iii. Hoye's approach to cylindrocyclophane A	64
iv. Smith's synthesis of cylindrocyclophanes A and F	69
III. First-Generation Approach to Cylindrocyclophane F.....	75
i. Suzuki cross-couplings of aryltrimethylanilinium salts.....	75
ii. B-alkyl Suzuki cross-coupling investigations	77
iii. Proposed catalytic cycle to explain nickel-catalyzed demethylation	81
iv. Retrosynthetic strategy for cylindrocyclophane F	85
v. Synthesis of a dimerization precursor	86
vi. Myers' reductive alkylation strategy.....	90
vii. Wittig olefination strategy	92
viii. Julia-Lythgoe olefination strategy.....	95

III. Second-Generation Approach to Cylindrocyclophane F	102
i. Revised retrosynthetic strategy.....	102
ii. Investigations into the Suzuki dimerization.....	104
iii. Reassessment of the <i>B</i> -alkyl Suzuki cross-coupling	108
Conclusion	111
Supporting Information.....	112

Chapter 4: Progress Towards the Total Synthesis of Cylindrocyclophane A: Cross-Coupling with an Alkenyl Potassium Trifluoroborate Salt.

I. A New Synthetic Target: Cylindrocyclophane A	143
i. Revisiting the cross-coupling of trimethylanilinium salts	143
ii. Retrosynthetic strategy for cylindrocyclophane A	145
II. Organocatalytic 1,4-Hydride Reduction of C_2C_2 -Unsaturated Aldehydes	147
III. Synthesis of Potassium Trifluoroborate Cross-Coupling Substates	152
i. Electron-withdrawing protecting group strategy	153
ii. A bulky silyl group as a choice of protecting group.....	155
iii. Ethers as base-stable protecting groups	157
iv. Isoprenyl functionality in the cross-coupling.....	163
IV. Synthesis of Trimethylanilinium Salts with Different Functionalities	165
i. Protected alcohols as oxidation state surrogates	165
ii. Electron-withdrawing group on the alkyl chain.....	171
iii. Simple alkenyl functionality on the alkyl chain	172
V. Investigation into Suzuki Cross-Couplings with Fully Functionalized <i>N,N,N</i> -Trimethylanilinium Triflates	175
i. Cross-coupling with substitution in the 4-position	176
ii. Exploration into the role of functionality on the anilinium salt.....	177
Conclusion	183
Supporting Information.....	184

Chapter 5: A Formal Synthesis of Cylindrocyclophane A.

I. Revisiting the olefin isomerization problem.....	221
i. Trimethylanilinium salt	221
ii. Transmetalation partner.....	222

II. Progress Towards the Total Synthesis of Cylindrocyclophane A.....	225
i. Retrosynthetic Strategy.....	225
ii. Stille cross-coupling with trimethylanilinium salt 1	226
iii. Diastereoselective allylic alkylation with chiral hydrazones.....	230
iii. Asymmetric allylic alkylation using the Tsuji reaction	230
III. A Formal Synthesis of Cylindrocyclophane A	240
Conclusion.....	245
Supporting Information.....	246

List of Schemes

Chapter 2: Total Synthesis of the Spiculisporic Acids: Exploitation of the Organocatalytic Vinylogous Mukaiyama-Michael Addition.

<i>Number</i>	<i>Page</i>
1. Preparation of 5-carboxyl-2-siloxyfurans	26
2. Preparation of siloxyfurans 21	27
3. Completion of (+)- <i>epi</i> -spiculisporic acid	31
4. Completion of (+)-spiculisporic acid	35

Chapter 3: Progress Towards the Total Synthesis of Cylindrocyclophane F: Investigations into a Novel B-alkyl Suzuki Cross-Coupling.

<i>Number</i>	<i>Page</i>
1. Synthesis of radical coupling precursors	60
2. Attempts at a free radical-mediated macrocyclization	61
3. Synthesis of macrocyclic Alder-Ene precursors.....	63
4. Installation of chiral butyl group via an Ireland-Claisen rearrangement.....	67
5. Synthesis of saturated phosphonate ester 45	68
6. Hoye's endgame approach to cylindrocyclophane A	69
7. Smith's first-generation approach to cylindrocyclophane F.....	70
8. Synthesis of cyclobutene 60	71
9. Synthesis of siloxyacetylene 56	72
10. Elaboration to an RCM dimerization precursor.....	73
11. Smith's second-generation endgame approach to the cylindrocyclophanes.....	74
12. Synthesis of trimethylanilinium salt.....	78
13. Undesired oxidation products of furan oxidation protocols.....	89
14. Successful ozonolysis of the furan to give acid 83	90
15. First-generation Wittig olefination.....	93
16. Second-generation Wittig olefination	94
17. Oxidation sequence forms <i>N</i> -oxide.....	97
18. Synthesis of phenyl sulfone 101	97

19. Synthesis of chiral aldehyde 107a for use in the Julia olefination	98
20. Julia olefination two-step sequence	100
21. Successful synthesis of a dimerization precursor	103
22. Key Suzuki cross-coupling dimerization sequence	107

Chapter 4: Progress Towards the Total Synthesis of Cylindrocyclophane A: Cross-Coupling with an Alkenyl Potassium Trifluoroborate Salt.

<i>Number</i>	<i>Page</i>
1. Synthesis of (<i>E</i>)- and (<i>Z</i>)-alkynyl enals	151
2. Preparation of vinyl iodides with electron-withdrawing groups	153
3. Preparation of vinyl iodide with TBDPS protecting group	156
4. Preparation of vinyl iodide with benzyl ether protecting group	158
5. Alternative route to chiral BF_3K salts	161
6. Synthesis of isoprenyl vinyl iodide via chiral auxiliary	164
7. Preparation of trimethylanilinium salts 39	166
8. Synthesis of a benzyl protecting anilinium salt	170
9. Installation of a dimethyldioxolane protecting group	172
10. Synthesis of methylene trimethylanilinium salt 50	173
11. Synthesis of trimethylanilinium triflate with extended terminal olefin	180

Chapter 5: A Formal Synthesis of Cylindrocyclophane A.

<i>Number</i>	<i>Page</i>
1. Synthesis of an allyl enol carbonate for AAA studies	238
2. Successful Tsuji-Trost allylic alkylation	241
3. Latest metathesis technology was ineffective for RCM dimerization	242

List of Figures

Chapter 1: Enantioselective LUMO-Lowering Organocatalysis.

<i>Number</i>	<i>Page</i>
1. Lewis-acid catalysis of the Diels-Alder reaction.....	5
2. Complimentary modes of LUMO-lowering catalysis.....	6
3. Iminium geometry control with imidazolidinones	6
4. Enantiofacial discrimination of chiral imidazolidinones.....	7
5. Calculated minimized structures for the iminium in figure 4.....	8
6. Easy access to imidazolidinones	8
7. Imidazolidinones developed and used within the MacMillan group	9

Chapter 2: Total Synthesis of the Spiculisporic Acids: Exploitation of the Organocatalytic Vinylogous Mukaiyama-Michael Addition.

<i>Number</i>	<i>Page</i>
1. Butanolides in natural products.....	12
2. Syntheses of the butanolide architecture.....	13
3. Lewis acids promote a Mukaiyama-Aldol addition	16
4. 1,2-addition versus 1,4-addition in the presence of chiral amines	18
5. Consumption of water in the catalytic cycle.....	19
6. Restoration of the catalytic cycle by protic nucleophiles	20
7. Spiculisporic acid and secospiculisporic acid.....	24
8. pH-Dependent molecular aggregation of the amine salts of spiculisporic acid.....	24
9. Brandænge's synthesis of spiculisporic acid	25
10. Retrosynthetic analysis of spiculisporic acid.....	25
11. Unsuccessful strategies for olefination	30
12. Possible transition states for organocatalytic Mukaiyama-Michael.....	36
13. Dipole interactions in the transition state.....	38
14. Transition state with <i>tert</i> -butyl-4-oxobutenoate	39
15. Electronic contributions to the transition state.....	41

16. 5-methyl ester versus 5-methyl siloxyfuran.....	42
17. Possible endo and exo transition states.....	43

Chapter 3: Progress Towards the Total Synthesis of Cylindrocyclophane F: Investigations into a Novel B-alkyl Suzuki Cross-Coupling.

Number	Page
1. Structures of the cylindrocyclophanes and nostocyclophanes	54
2. X-ray structure of nostocyclophane D	55
3. Proposed biosynthetic pathway.....	56
4. Albizati's equilibration hypothesis for the cylindrocyclophanes	58
5. Albizati's retrosynthetic analysis of the model system	59
6. Trost's retrosynthetic analysis of cylindrocyclophane A	62
7. Hoye's retrosynthetic analysis of cylindrocyclophane A	65
8. Unsuccessful incorporation of the butyl group.....	66
9. Smith's retrosynthetic plan for cylindrocyclophanes A and F	71
10. RCM dimerization to form the cylindrocyclophane macrocycle	74
11. Ineffective transmetalating partners in the cross-coupling reaction.....	81
12. Proposed catalytic cycle for <i>B</i> -alkyl Suzuki cross-coupling	82
13. Nickel-catalyzed demethylation of trimethylanilinium salt	83
14. Charge distribution in the tetramethylammonium ion.....	84
15. Competing oxidative addition pathways on trimethylanilinium salts.....	84
16. Retrosynthetic plan	85
17. Myers' reductive alkylation mechanism	91
18. The Julia olefination	95
19. Mechanism of the Kowalski rearrangement	99
20. Proposed mechanism for cleavage of acetoxy sulfones	101
21. An unreactive intermediate under one-electron reducing conditions.....	101
22. Alternative retrosynthetic strategy	102
23. Access to \square -stereogenicity on the alkyl borane	105
24. Lithiation/transmetalation preparation of alkyl boranes in natural product synthesis	106
25. Boron NMR chemical shifts.....	110

Chapter 4: Progress Towards the Total Synthesis of Cylindrocyclophane A: Cross-Coupling with an Alkenyl Potassium Trifluoroborate Salt.

<i>Number</i>	<i>Page</i>
1. Transmetalation reagents operable with Ni(0) cross-coupling.....	144
2. Lack of diastereoccontrol in an alkylation of the macrocycle.....	145
3. Retrosynthetic plan for cylindrocyclophane A	146
4. Hantzsch ester as a biologic mimetic for NADH	148
5. Catalyst-assisted isomerization of C_2C_2 -unsaturated aldehydes.....	149
6. Sterics was the dominating factor in the iminium olefin isomerization.....	152
7. Unsuccessful attempts to functionalize the terminal alkyne	159
8. Intramolecular trap of ether oxygen onto the alkyne.....	160
9. Facilitation of a transmetalation event with a pendant isoprenyl group.....	163
10. Dimethylaniline versus phenylpyrrolidine.....	167
11. Location of a hydrogen bond on dimethylaniline and phenylpyrrolidine.....	168
12. Cross-coupling with a pyridino-anilinium salt.....	169
13. Isolated side-products of the cross-coupling in equation 17	171
14. A non-productive route with the current cross-coupling strategy	175
15. Substitution in the 4-position of the anilinium salt was tolerated	177
16. Possible directing of the nickel by an olefin on the alkyl chain	179
17. Decreased directing capability with a more substituted olefin.....	182

Chapter 5: Formal Synthesis of Cylindrocyclophane A.

<i>Number</i>	<i>Page</i>
1. A selective olefination isomerization required for further functionalization.....	223
2. Revised retrosynthetic plan	225
3. An achiral allylation for an assay.....	229
4. Allylic alkylation with a chiral auxiliary to facilitate determination of diastereoselectivity.....	230
5. SAMP-hydrazone alkylations in natural product synthesis.....	231
6. Diastereoselective alkylation of SAMP hydrazone	232
7. Addition to C=N bond in the diastereoselective alkylation.....	235
8. AAA of cyclic ketones by Stoltz and Trost	237

9. Trost's AAA of acyclic systems	237
10. Remaining synthetic sequence to the natural product	243
11. Completion of the synthesis of cylindrocyclophane A.....	244

List of Tables

Chapter 2: Total Synthesis of the Spiculisporic Acids: Exploitation of the Organocatalytic Vinyllogous Mukaiyama-Michael Addition.

<i>Number</i>	<i>Page</i>
1. The effect of protic sources in the organocatalytic Mukaiyama-Michael reaction.....	21
2. Organocatalyzed addition of siloxyfurans into α,β -unsaturated aldehydes.....	22
3. Organocatalyzed addition of siloxyfurans into crotonaldehyde.....	23
4. Examination of acid co-catalyst.....	28
5. Examination of solvents with triflic acid as the co-catalyst	29
6. Examination of solvents in the presence of weaker acidic co-catalysts.....	32
7. Effect of polar solvents on diastereoselectivity of adduct 31	34

Chapter 3: Progress Towards the Total Synthesis of Cylindrocyclophane F: Investigations into a Novel B-alkyl Suzuki Cross-Coupling.

<i>Number</i>	<i>Page</i>
1. Base screen for cross-coupling with model system.....	79
2. Ligand screen in the cross-coupling.....	80
3. Solvent screen for organocatalytic aniline addition.....	87
4. Representative co-catalyst screen.....	87
5. Survey of a combination of co-catalyst and solvent conditions.....	88
6. Probing the counterion effect in the Suzuki cross-coupling.....	109

Chapter 4: Progress Towards the Total Synthesis of Cylindrocyclophane A: Cross-Coupling with an Alkenyl Potassium Trifluoroborate Salt.

<i>Number</i>	<i>Page</i>
1. Phenylboronic acid Suzuki cross-couplings with various anilinium salts	178
2. Testing the directing effect of pendant olefins on the aliphatic side chain	182

Chapter 5: Formal Synthesis of Cylindrocyclophane A.

<i>Number</i>	<i>Page</i>
1. Trimethylanilinium salts that can participate in the cross-coupling.....	222
2. Survey of fluoride sources in the Stille cross-coupling.....	228
3. Diastereoselective alkylation with SAMP-hydrazone.....	233
4. Diastereoselective alkylation with SAPP-hydrazone 1	234
5. Asymmetric allylic alkylation of model system 27	239

ABBREVIATIONS

acac	acetylacetone
Ac₂O	acetic anhydride
AcCl	acetyl chloride
AcOH	acetic acid
AIBN	azabis(isobutyronitrile)
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	<i>tert</i> -butyl carbamate
BOM	benzyloxymethyl
BOM-Cl	benzyloxymethyl chloride
Bpin	pinacolatoboron
BPS	<i>tert</i> -butyldiphenylsilyl
Bz	benzoyl
Bu	butyl
COD	cyclooctadiene
Cp*	pentamethylcyclopentadiene
dba	dibenzylideneacetone
DCA	dichloroacetic acid
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIP-Cl	<i>B</i> -chlorodiisopinocampheylborane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DNBA	2,4-dinitrobenzoic acid

dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphine)propane
EtOAc	ethyl acetate
GC	gas chromatography
Glu	glucosyl
h	hour
HOMO	highest occupied molecular orbital
HPLC	high pressure liquid chromatography
IC₅₀	concentration necessary for 50% inhibition
IMes • HCl	1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride
imid	imidazole
IpcBH₂	isopinocamphenylborane
IPr • HCl	1,3-bis(2,6-diisopropylphenyl)imidazolium chloride
LA	Lewis acid
LDA	lithium diisopropylamine
LiHMDS	lithium hexamethyldisilamide
LiTMP	lithium 2,2,6,6-tetramethylpiperidine amide
LUMO	lowest unoccupied molecular orbital
MCA	monochloroacetic acid
MeOH	methanol
MeOTf	methyl trifluoromethanesulfonate
min	minutes
MOM	methoxymethyl
NADH	nicotinamide adenine dinucleotide
NBA	2-nitrobenzoic acid
NMO	<i>N</i> -methylmorpholine-4-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect

Nu	nucleophile
OBBD	10-bora-9-oxabicyclo[3.3.2]decane
PCy₃	tricyclohexylphosphine
PHOX	phosphinooxazoline
Piv	trimethylacetyl
PMB	<i>para</i> -methoxybenzyl
ppm	parts per million
PT	5-phenyltetrazole
<i>p</i>-TSA	<i>para</i> -toluenesulfonic acid
Pyr	pyridine
R_L	R _{LARGE}
R_S	R _{SMALL}
RAMP	(<i>R</i>)-1-amino-2-methoxymethylpyrrolidine
RCM	ring-closing metathesis
SAEP	(<i>S</i>)-1-amino-2-(1-ethyl-1-ethoxypropyl)pyrrolidine
SAMP	(<i>S</i>)-1-amino-2-methoxymethylpyrrolidine
SAPP	(<i>S</i>)-1-amino-2-(1-propyl-1-ethoxypropyl)pyrrolidine
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium triphenyldifluorosilicate
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBDPSCI	<i>tert</i> -butylchlorodiphenylsilane
TBS	<i>tert</i> -butyldimethylsilyl
TBSCl	<i>tert</i> -butylchlorodimethylsilane
TBSOTf	<i>tert</i> -butyldimethylsilyl trifluoromethanesulfonate
TCA	trichloroacetic acid
TES	triethylsilyl
TESCl	chlorotriethylsilane
TFA	trifluoroacetic acid

TFE	2,2,2-trifluoroethanol
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	chlorotrimethylsilane
TPAP	tetrapropylammonium perruthenate
X_C	chiral auxiliary

To Mom