ZIRCONIUM-CATALYZED ASYMMETRIC CARBOALUMINATION OF α-OLEFINS

by

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Coordinatively unsaturated alkylzirconocene derivatives can undergo stereo-, and regioselective carbometallation reactions. The Zr-catalyzed carboalumination of alkynes has been widely explored and developed into a general reaction of high synthetic utility, and it has been applied to the synthesis of numerous complex natural products. Highly promising is the Zr-catalyzed asymmetric carboalumination of alkenes developed by Negishi and Kondakov. The reaction suffers from a few critical deficiencies, mainly the modest level of asymmetric induction, especially the 70-80% ee range obtained in most of the reactions. Further improvements in % ee will depend on the development of effective zirconocene catalysts.

As part of our program to enhance the scope of organozirconium chemistry in organic synthesis, we focused on examining homogeneous zirconocenes and other zirconium-containing non-metallocenes for the catalytic asymmetric carbometalation of α-olefins.

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ABBREVIATIONS

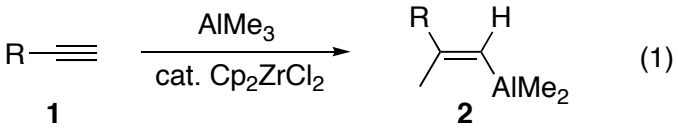
Ac	Acetyl
AlR_3	Trialkylaluminum
DCC	1,3-Dicyclohexylcarbodiimide
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	*N,N*-Dimethylformamide
dr	Diastereomeric ratio
ee	Enantiomeric excess
HMPA	Hexamethylphosphoramide
KHMDS	Potassium *bis*(trimethylsilyl)amide
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyldisilazide
MAO	Methylaluminoxane
MTPA	α-Methoxy-α-(trifluromethyl)phenylacetic acid
Mes	Mesityl
NBS	*N*-Bromosuccinimide
TEBA	Benzyl triethylammonium chloride
TBDPS	*tert*-Butyldiphenylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMSCl	Trimethylsilyl chloride

TsOH	*p*-Toluenesulfonic acid
Py	Pyridine

1.0 INTRODUCTION

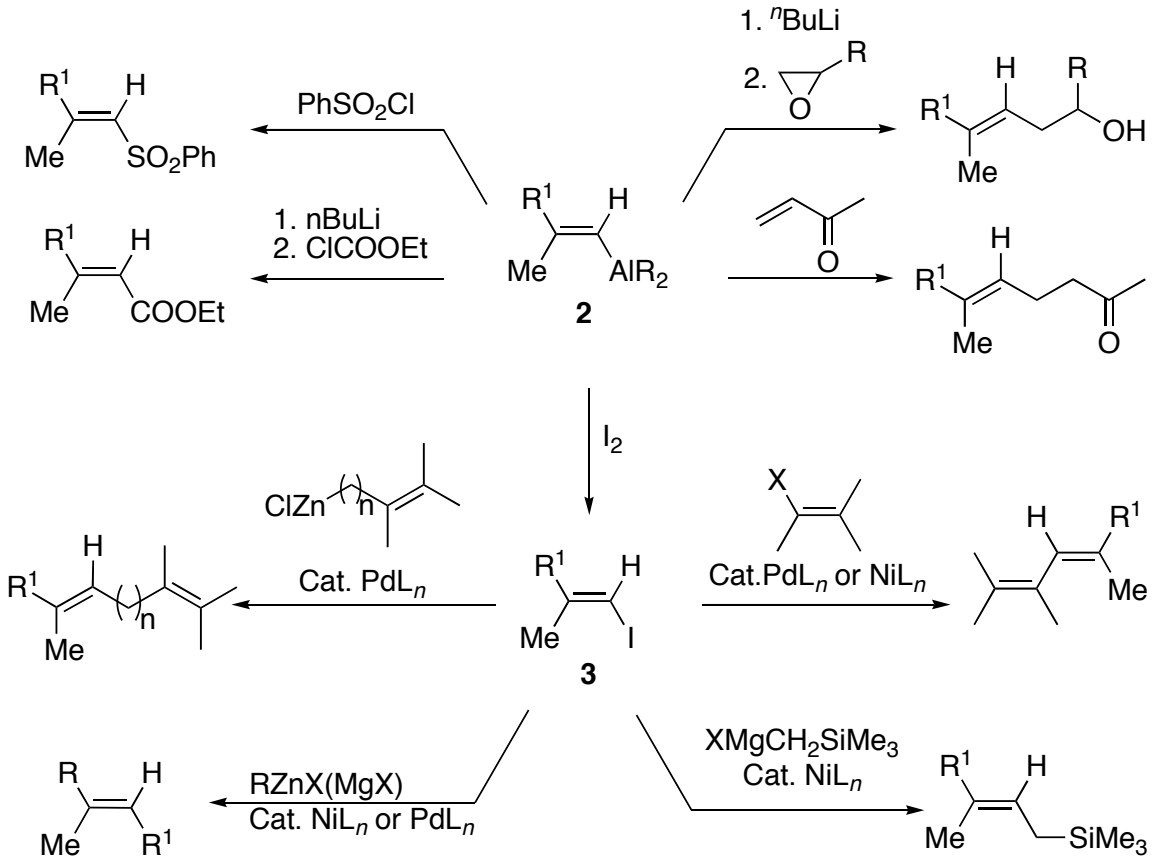
1.1 Zr-CATALYZED CARBOALUMINATION OF ALKYNES

In 1978, Negishi and Van Horn introduced the Zr-catalyzed carboalumination of alkynes (Equation 1).[1] Initially, the reaction was thought to be stoichiometric in Cp_2ZrCl_2 and, it was later discovered to be catalytic.[2] The mechanism and the regioselectivity of this reaction has been widely studied.[3,4,5,6,7,8,9,10] This method of carbon-carbon bond formation *via* alkylalanes has been used in multiple synthetic applications and has been shown to be compatible with a wide range of functional groups, including hydroxyl groups, silyl ether protecting groups, halogens, alkenes and arenes.



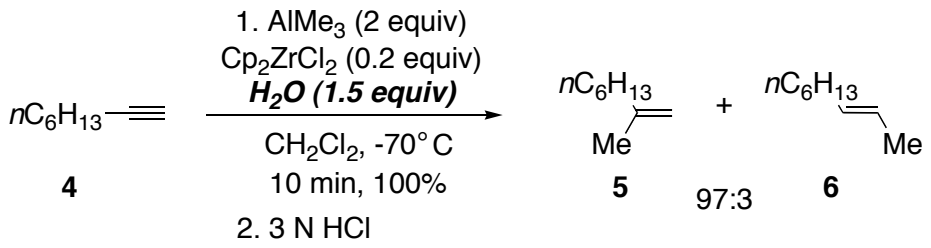
1 **2** (1)

Negishi has demonstrated that the vinylalane intermediates can be synthetically useful reagents. For example, these vinylalanes are readily amenable to Pd(0) or Ni(0)-catalyzed cross-coupling reactions with alkenyl or arylhalides or they can be trapped with a range of electrophiles, including alkyl halides, chloroformates, epoxides, aldehydes and enones (Scheme 1).[11]



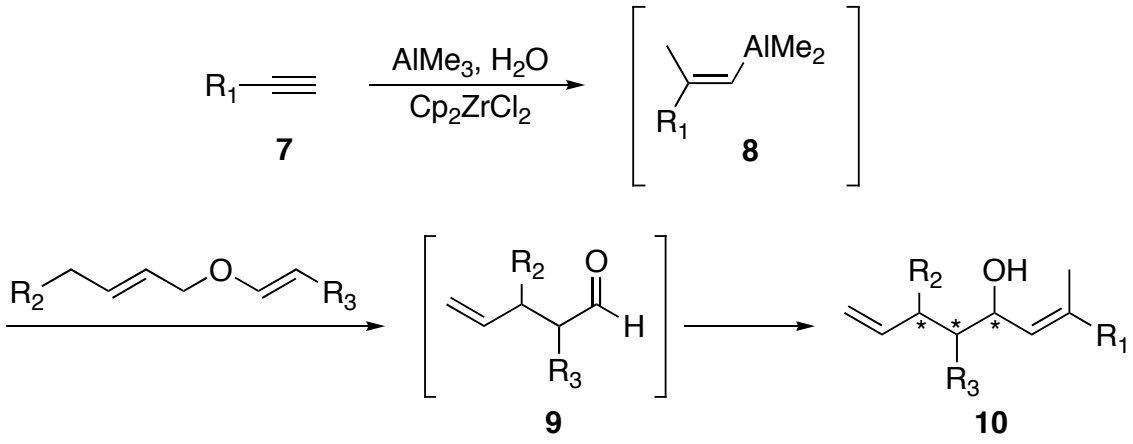
Scheme 1. Conversion of (*E*)-2-methyl-1-alkenylalanes into various synthetically useful products.

In 1993, Wipf and Lim demonstrated that additives such as MAO and water provide considerable rate-enhancing effects in the Zr-catalyzed carboalumination of alkynes.[12,13] This method was later extended to α-olefins (*vide infra)*.[14,15] Under standard Negishi conditions, 1-octyne carboaluminates in 3 h at room temperature to give **5** and **6** in a 95:5 mixture of regioisomers. Addition of stoichiometric amounts of water allows for the same carboalumination to take place within minutes at -70 °C and produces a 97:3 mixture of regioisomers. This selectivity is slightly higher than the one reported by Negishi (Scheme 2).



Scheme 2. Water accelerated carboalumination of alkynes.

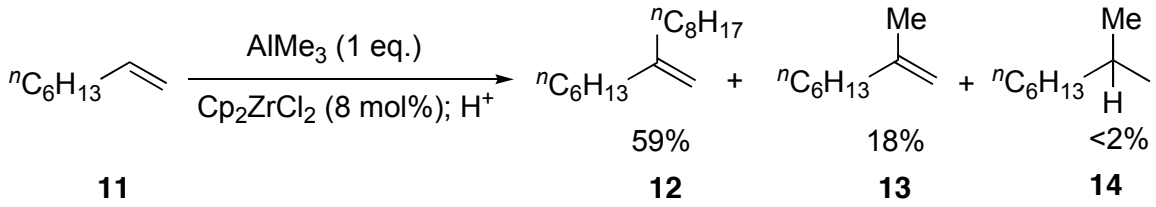
Wipf, Nunes and Ribe extended this methodology to the *in situ* addition of vinyl alanes to aldimines.[13] More recently, this methodology was used in a three-step cascade reaction involving water-accelerated catalytic carboalumination, a Claisen rearrangement, and a nucleophilic carbonyl addition, converting terminal alkynes and allyl vinyl ethers into allylic alcohols containing up to three contiguous asymmetric centers (Scheme 3).[16]



Scheme 3. Cascade conversion of alkynes into allylic alcohols.

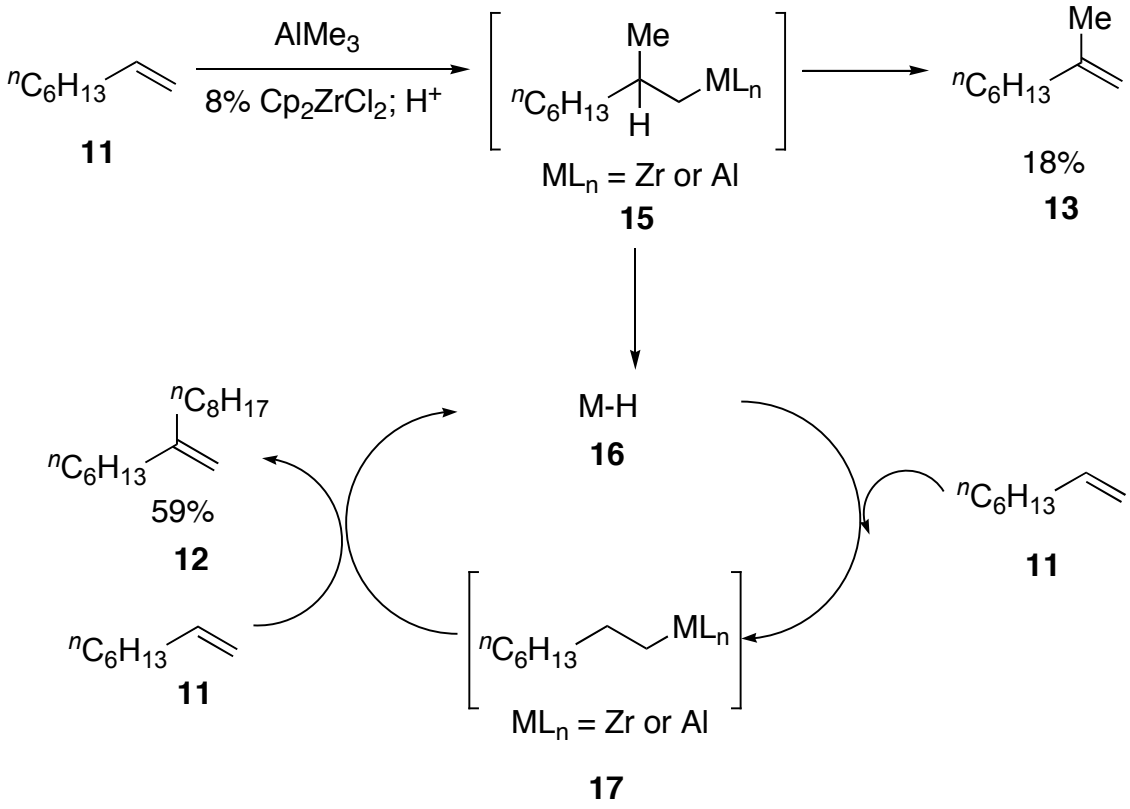
1.2 Zr-CATALYZED CARBOALUMINATION OF ALKENES

Despite the success of the Zr-catalyzed carboalumination of alkynes, the analogous transformation with alkenes was initially not successful, leading only to trace amounts of the desired products. For example, submitting 1-octene **11** to the standard carboalumination conditions (i.e. 1 equiv. of $AlMe_3$ and 8 mol% of Cp_2ZrCl_2) led to the product distribution shown in Scheme 4.[17]



Scheme 4. Product distribution in Negishi's initial attempt at olefin methylalumination.

The proposed pathway leading to the product distribution for 1-octene **11** and $AlMe_3$ is shown in Scheme 5. The initially formed 2-methyloctylmetal intermediate **15** readily undergoes β-H elimination, leading to **14** (2-methyl-1-octene) and metal hydride intermediate **16**. Hydrometallation of **11** leads to intermediate **17**, which is then transferred *via* carboalumination to **11**, resulting in **12** (Scheme 5).

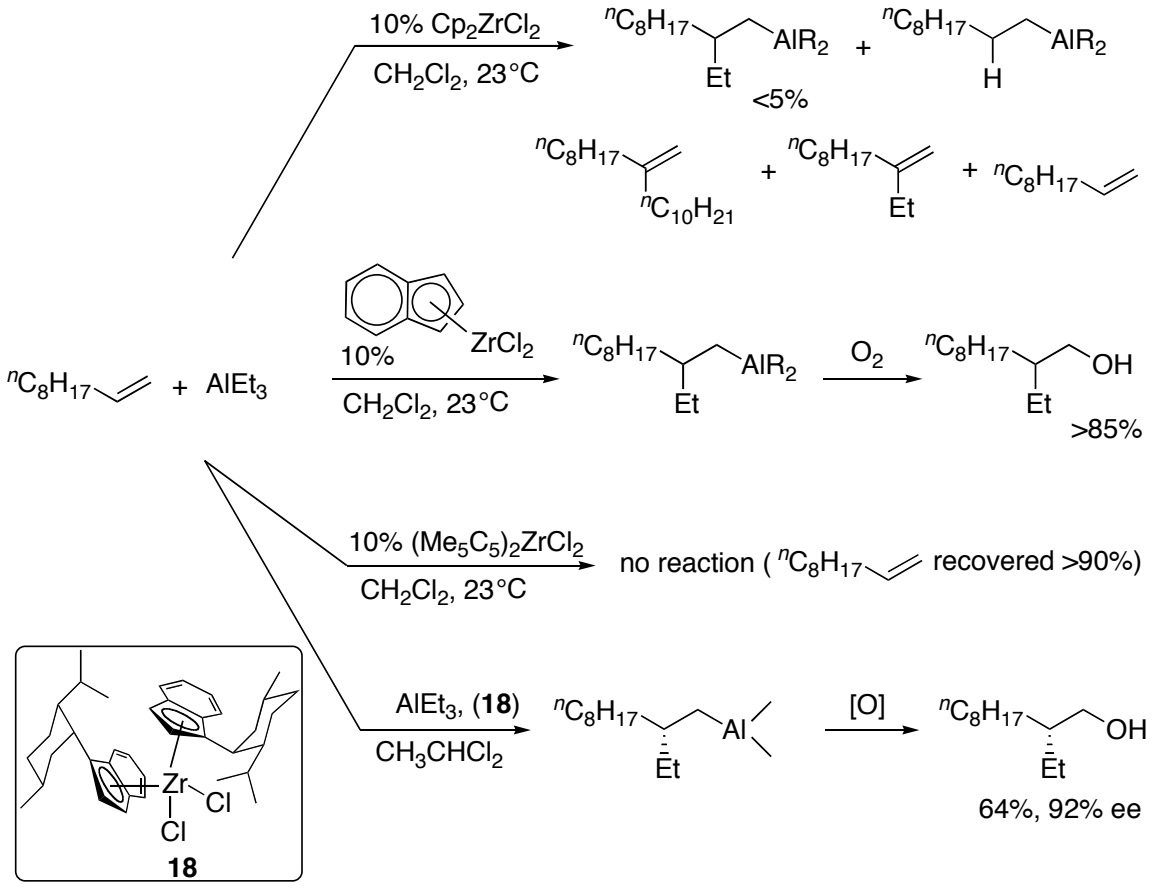


Scheme 5. Proposed pathway for the formation of major products 12 and 13.

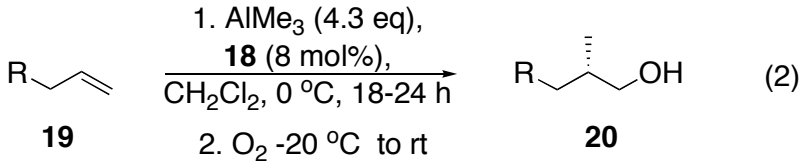
Based on these experimental results, Negishi concluded that oligomerization of the starting alkenes, β-H transfer, and hydrometallation could deplete the desired metallation product, the latter being the most predominant. Investigations of Zr-catalyzed hydroalumination with $Al^{i}Bu_3$ shed light on this mechanism and verified hydrometalation as a side reaction.[18] Additionally, cyclic carbozirconation appears to limit the scope of alkylalumination with longer alkyl chains.

In view of these observations, it appeared that suppressing β-hydride elimination would provide selectivity in the carboalumination of alkenes. To some extent this was achieved through the use of bulky indene derivatives in place of the cyclopentadiene ligands (Scheme 6).[19] Further, the indene core has been incorporated with chiral

substituents in Erker's catalyst **18**.[20] This complex mediates the most enantioselective carboalumination of terminal olefins that has been reported to date.



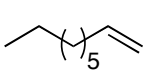
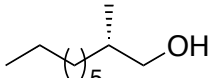
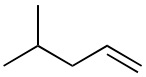
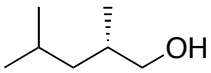
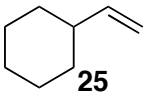
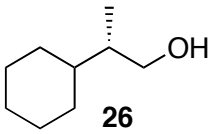
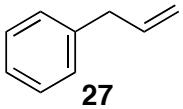
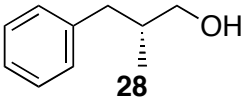
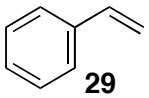
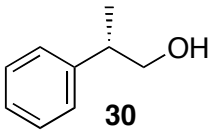
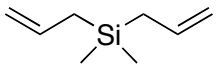
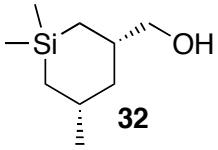
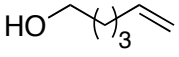
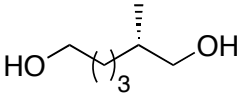
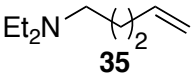
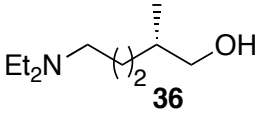
Scheme 6. Zr-catalyzed ethylalumination of decene with different metallocenes.



The preliminary results of methylalumination of α-olefins using 8 mol% of catalyst **18**, and 1 equiv. of $AlMe_3$ afforded chiral 2-methyl-1-alkanols **20** in good enantiomeric excess and isolated yields (Equation 2 and Table 1). From this data, it appears that the

bulky menthol substituent on the indene ligand suppressed the undesired β-hydride elimination (Scheme 5).

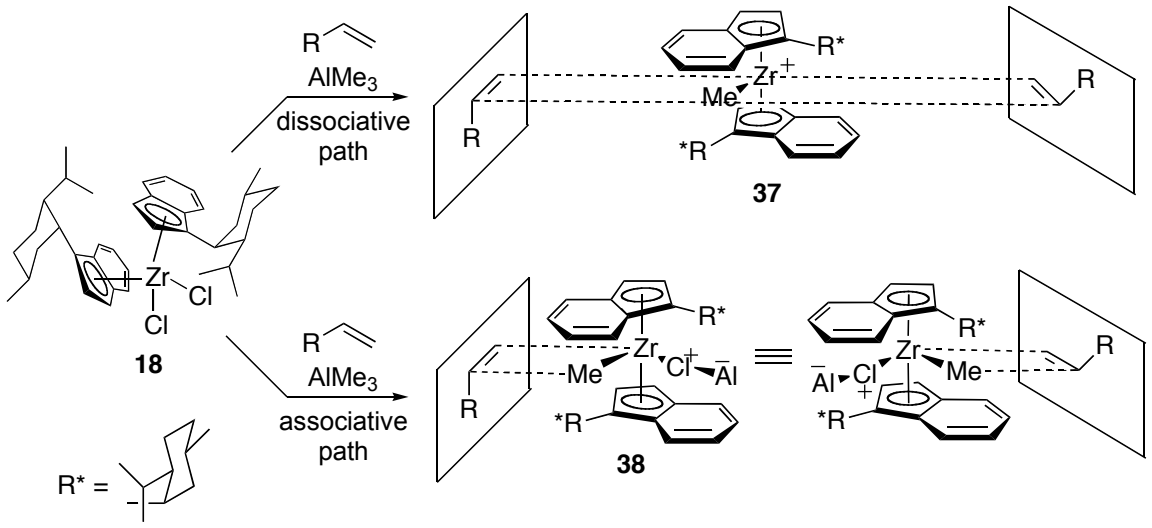
Table 1. Zirconium-catalyzed asymmetric methylalumination of α-olefins.

Entry	Alkene	Time (h)	Product	Yield (%)[a]	ee (%)[b]
1	 **21**	12	 **22**	88	72
2	 **23**	12	 **24**	92	74
3	 **25**	12	 **26**	80	65
4	 **27**	24	 **28**	77	70
5	 **29**	528	 **30**	30	85
6	 **31**	12	 **32**	81	74
7	 **33**	12[c]	 **34**	79	75
8	 **35**	96[d]	 **36**	68	71

[a]Yields are based on isolated, and pure materials; [b]ee's Determined by Mosher ester analysis (^{1}H NMR); [c]Three fold excess of $AlMe_3$ was used; [d]Two equivalents of $AlMe_3$ were used.

As shown in Table 1, the reaction conditions were compatible with several functionalities including straight chain aliphatic and β- or α-branched, alkylsilanes, free alcohols and tertiary amines. Enantiomeric excess ranged from 65 to 74% (Entries 1-3). In the case of styrene, the reaction proceeded in 30% yield after 22 days (Entry 5); polymerization was observed as a side reaction.

The observed high enantiomeric excess was difficult to explain in terms of a direct formation of the Me-Al bond assisted by zirconocene as suggested in the Zr-catalyzed methylalumination of alkynes.[1,2] In contrast, these results appeared to be consistent with direct Me-Zr bond addition promoted by an organoaluminium species in accordance with the accepted mechanism for the homogeneous Ziegler-Natta type reaction.[21] Based on the uniformly observed (*R*)-configuration of 2-methyl-1-alkanols **20** and the conformation of catalyst **18**,[17,22] a four center *syn* Me-Zr addition was feasible, and it conferred further support for the direct Me-Zr bond addition mechanisms (Scheme 7). In the transition states **37** and **38**, both the Zr-Me σ-orbital and the empty zirconium *d*-orbitals are on the front side. Thus, in terms of catalyst topology, only two quadrants are accessible to an approaching olefin. This trajectory allows the menthol auxiliary to dictate the olefin orientation as it approaches the metal. The proposed transition state leads to a Zr-alkene interaction on the *re*-face and subsequent formation of the observed 2-(*R*)-2-methyl-1-alkanol.



Scheme 7. Proposed transition state for zirconium-catalyzed enantioselective methylalumination of 1-alkenes with $AlMe_3$.

In 1996, Negishi and Kondakov reported the extension of this methodology to include higher alkylalanes.[23] The corresponding 2-ethyl-1-alkanols (Equation 2) were obtained in lower yields but in higher ee's than the methyl derivatives (see Table 2 for comparison). The ee's were also found to be significantly solvent dependent for both systems. The use of halogenated solvents (i.e CH_3CHCl_2 or CH_2Cl_2) improved the ee by ~10%.[24] One of the puzzling aspects of this transformation was the significantly lower enantioselectivity observed in methylalumination compared with ethylalumination (68 - 85% vs. 90 - 95% ee). One can surmise that under the influence of chiral ligands, agostic interactions involving α-CH bonds[25] can exert a secondary asymmetric induction effect with larger alkyl groups but not with methyl (Scheme 8).[26]

Table 2. Zr-catalyzed methyl- and ethylalumination-oxidation of alkenes.

		$AlMe_3$		$AlEt_3$	
Entry	Alkene	Yield (%)	ee (%)	Yield (%)	ee (%)
1	$^{n}CH_4H_9$-, $^{n}CH_6H_{13}$-, $^{n}C_8H_{17}CH=CH_2$	88	72	63-75	90-93
2	$^{i}BuCH=CH_2$(**39**)	92	74	77	90
3	$PhCH=CH_2$(**29**)	77	70	69	93
4	$HexCH=CH_2$ (**25**)	80	65		
5	$HO(CH_2)_4CH=CH_2$(**33**)	79	75	88	90
6	$Et_2N(CH_2)_3CH=CH_2$(**35**)	68	71	56	96

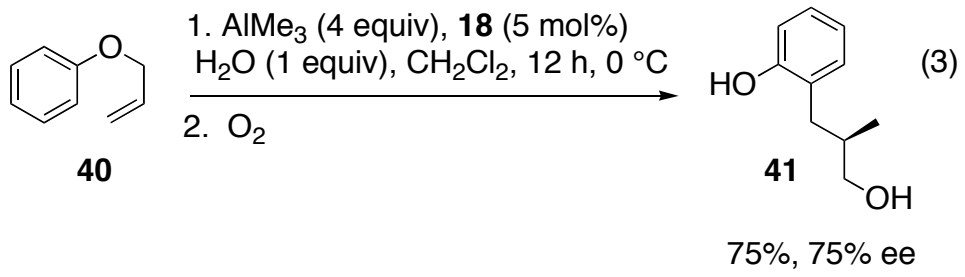
no asymmetric induction

possible asymmetric induction

Scheme 8. Secondary asymmetric induction derived from α-agostic induction.

Our group has demonstrated the enhancing effect of water in carboalumination of alkynes (*vide supra*). This concept was later extended to the Zr-catalyzed carboalumination of α-olefins, using 5 mol% of Erker's catalyst, 4-5 equiv of $AlMe_3$, and 1 equiv of H_2O.[14,15] The results obtained were comparable to those by Negishi and Kondakov.[17,23] The most dramatic rate enhancement observed was for the reaction with styrene; not only was the reaction completed in 12 h (vs. 22 days by the previous method), but the isolated yield was 73% and the product was observed in 89% ee compared to 30% yield and 85% ee. As demonstrated for alkynes, the organoalane intermediate was not quenched by hydrolysis. This modification was later used elegantly in a tandem process in which water accelerated a sigmatropic rearrangement and the subsequent carbometalation reaction, providing enantioenriched, polyfunctionalized scaffolds. For example, adding allyl phenyl ether **40** to a mixture of $AlMe_3$, Erker's

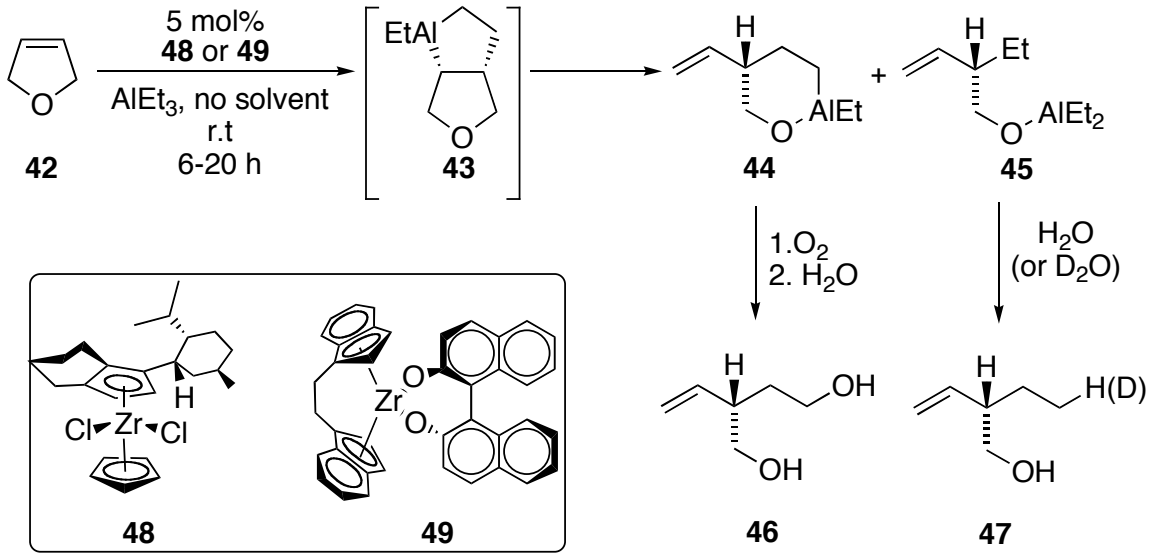
catalyst **18**, and H_2O in CH_2Cl_2 followed by oxidate workup afforded the Claisen rearrangement-methylalumination product **41** (Equation 3).[15]



40 **41** (3)

75%, 75% ee

Additionally, several other important developments have been reported relating to the metal-catalyzed alkylation of alkenes (other than unsaturated carbonyls or allylic esters).[27] Whitby reported that treatment of 2,5-dihydrofuran **42** with $AlEt_3$ in the presence of 5 mol% of complexes **48** or **49** led to the enantioselective formation of diol **46**, rather than the product obtained from catalytic carbomagnesations, which yielded monoalcohol **47**. The enantioselectivity observed with **49** was >99% ee, whereas that observed with **48** was 85-90% ee (Scheme 9).[28] Mechanistically, this process proceeds through aluminacyclopentane **43**, which is converted to the corresponding aluminaoxacyclohexane **44** through an undetermined mechanism. To ensure the predominant formation of **46**, catalytic alkylation must be carried out in the absence of solvent.



Scheme 9. Whitby's Zr-catalyzed enantioselective 2-ethylalumination of alkenes.

Although the synthetic potential of the Zr-catalyzed asymmetric carboalumination appears to be considerable, its application to the synthesis of natural products has been limited. Scyphostatin[29] and TMC-151 A-F[30] have been efficiently synthesized by Negishi and coworkers. A synthesis of pitiamide A was also achieved utilizing this methodology by Wipf *et al*.[31] (Figure 1).

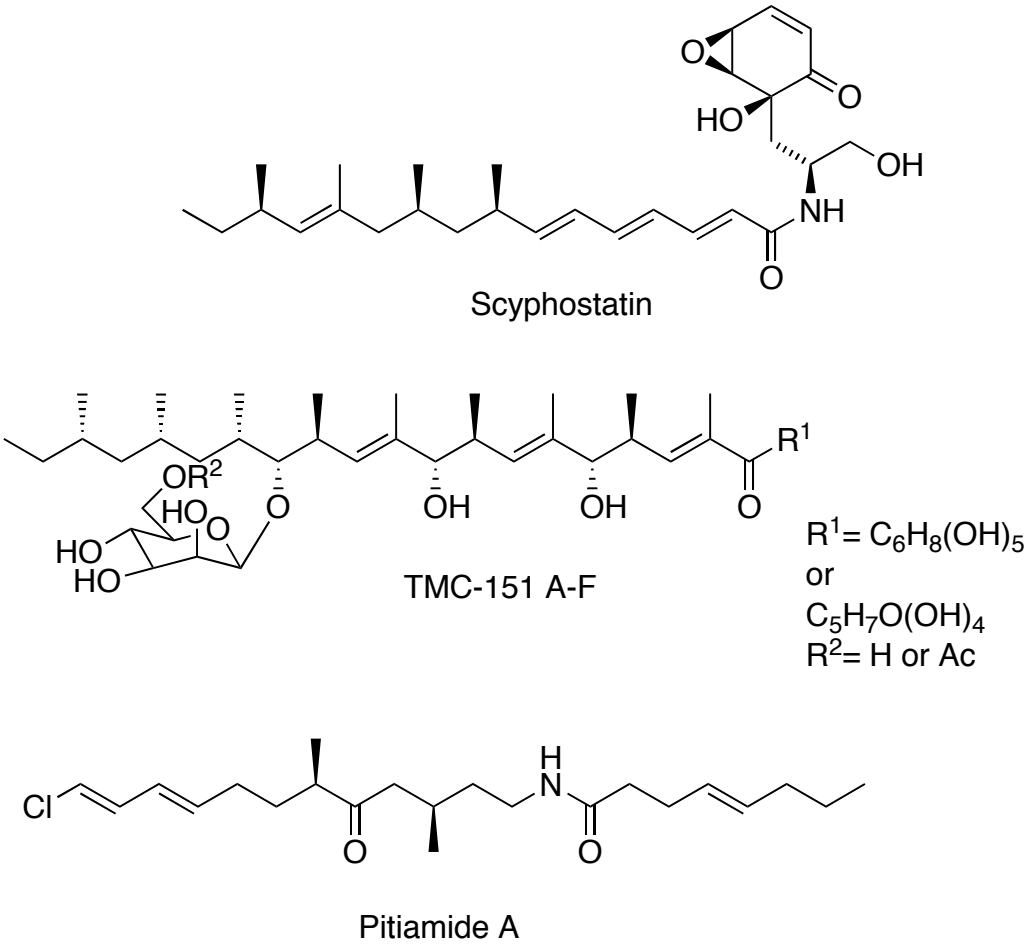


Figure 1. Selected natural products synthesized *via* a Zr-catalyzed carboalumination reaction.

Despite its novelty, reasonable generality, and considerable synthetic potential, the reaction suffers from several drawbacks, primarily the modest asymmetric induction, and to date no significant improvements have been realized. We have focused our efforts on the exploration of known zirconocenes that could potentially display activity in the catalyzed asymmetric carboalumination of α-olefins. Among the metallocenes disclosed in the literature, indene complexes have shown modest activity in the carbometalation of terminal and cyclic alkenes, including the previously disclosed Erker's catalyst **18** (Figure 2).[27]

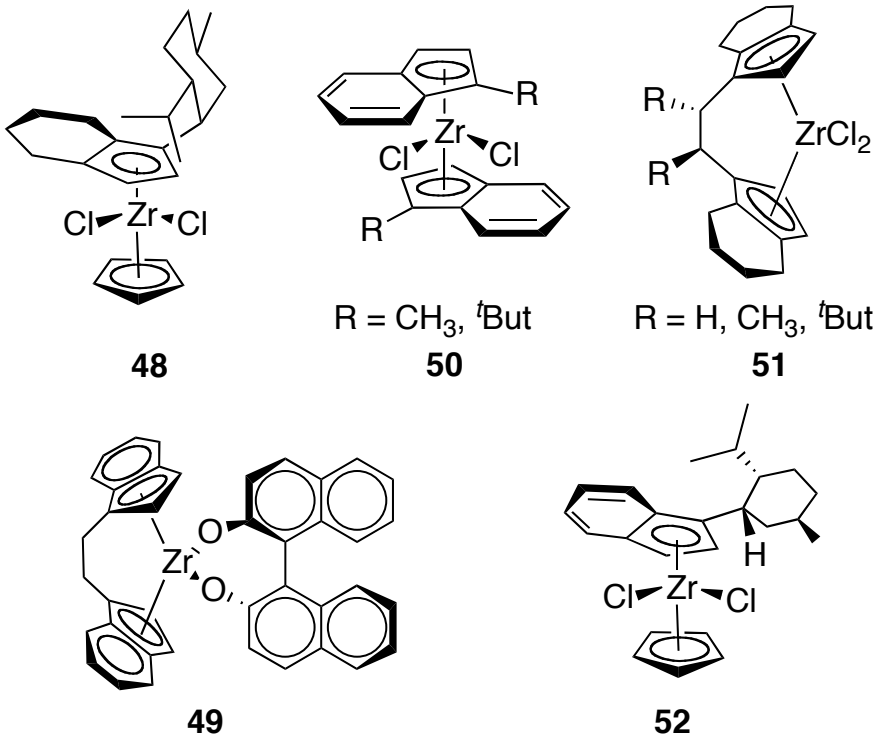


Figure 2. Metallocenes studied in the carboalumination of alkenes.

The employment of bis(η^5-cyclopentadienyl) ligands for introducing chirality is particularly attractive due to the wide variety of potential structural modifications on organometallic complexes containing this ligand, as well as the superior tenacity with which they attach themselves to transition metals (with dissociation energies up to 118 kcal/mol).[32] It is estimated that more than 80% of all known organometallic complexes of the transition metals contain the cyclopentadienyl fragment.[33]

A number of concepts have been used to interpret the influence of such ligands on the stability of the metal center and M-R bonds, and hence the catalytic activity. These include the σ-donor ability or basicity of the ligands, the π-acceptor strength of the ligands, the *trans* effect, the electronic density on the metal, and the energy of the orbitals. In a metallocene complex, such as Cp_2ZrCl_2, the π orbitals of the

two parallel $C_5H_5^-$ ligands yield three sets of orbitals: a low-lying filled pair of a_{1g} and a_{2u} symmetry, a set of filled orbitals, e_{1g} and $e_{1u,}$ and a high-lying empty set of antibonding orbitals of symmetry e_{2g} and e_{2u}. These orbitals interact with the orbitals of the metal (Figure 3).[34a] The strong interaction of the ligand orbitals with metal the *s*, *p* and the e_{g1} (d_{xz}, d_{yz}) orbitals provides a net stabilization to the metal center, The existence of stable isoelectronic diamagnetic complexes of Ti(IV), Zr(IV), Nb(IV) and Ta(IV) provides evidence for this stability.[34b]

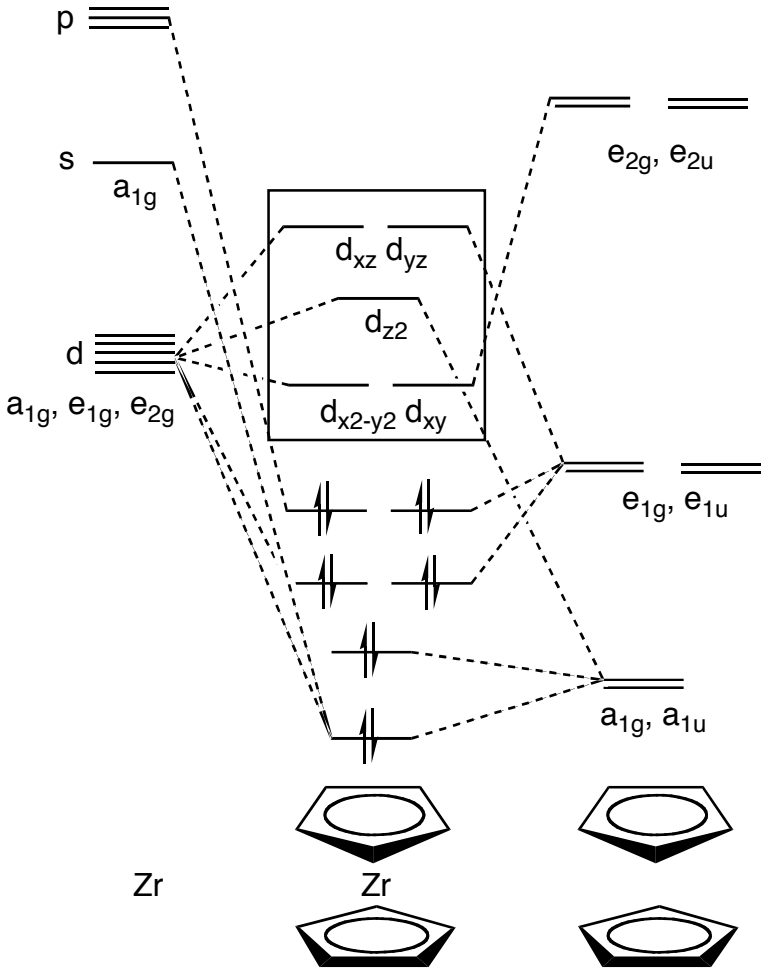


Figure 3. Molecular orbital diagram of Cp_2Zr (in square frontier orbitals).

The remaining three d orbitals of the metal, the a_{1g} (d_{Z2}) and the e_{2g} (d_{x2-y2}, d_{xy}) set, remain essentially nonbonding. In d^0 (16-electron) systems (e.g. Cp_2ZrCl_2), rehybridization of the remaining non-bonding orbitals generates three new, highly directed orbitals that point away from the C_5H_5 rings (Figure 4a).[35b] The steric requirements of these additional ligands force the Cp ligands to bend back. This allows the ligand donor orbitals to overlap effectively, therefore attaining maximum meta-ligand bonding. To obtain a favorable electron configuration, this class of complexes incorporates additional ligands that can contribute extra electrons (e.g. Cl^- or H^-). In the case of Cp_2ZrCl_2, one valance-shell empty orbital remains available for coordination, allowing it to act as a Lewis acid (Figure 4b).

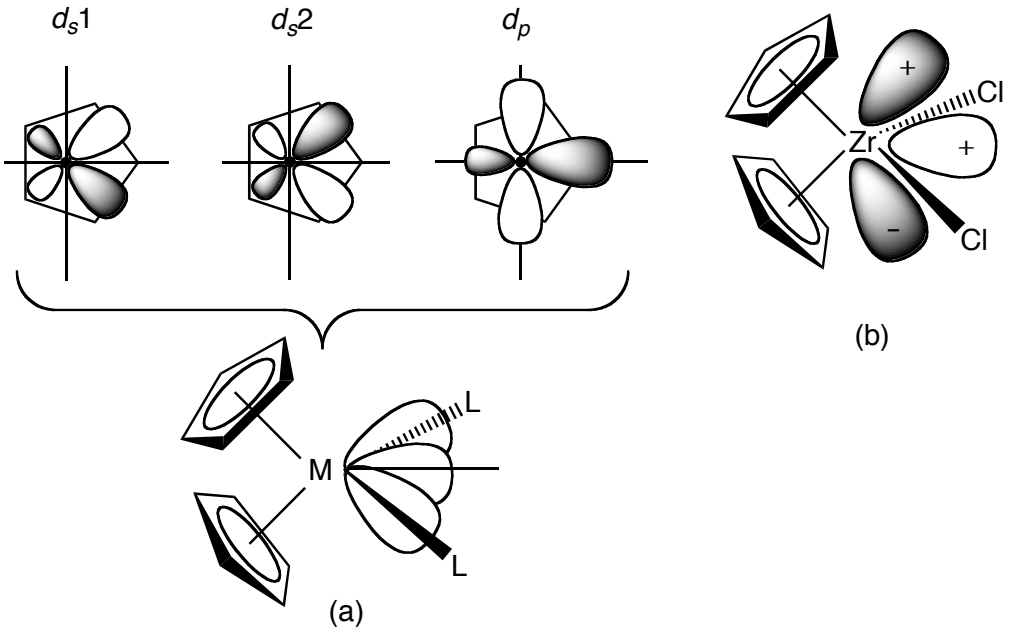


Figure 4. (a) Orientation of the frontier orbitals of a Cp_2ML_2 complex. (b) Available coordination sites of Cp_2ZrCl_2.

The reactions of 16-electron zirconocene derivatives are triggered by interaction of the empty orbital with electrons donors, including nonbonding electron pair donors, π-bonds or π-electrons, (e.g. hydrozirconation, carbonization and heterozirconation) and σ-bonds or σ-electrons (e.g. oxidative addition, σ-bond metathesis including transmetallation and migratory insertion).[35a]

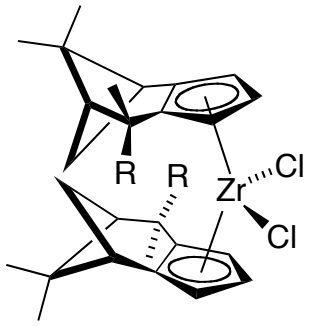
Among the small number of pre-catalysts which have been used successfully in polymerization,[36] hydrogenation,[37] cycloisomerization,[38] cycloamination,[39] and cyclohydrosilation,[40] we focused on examining homogenous zirconocenes and other zirconium-containing non-metallocenes for the catalytic asymmetric carbometalation of α-olefins.

In order to provide cyclopentadienyl ligands with well-defined asymmetry, the groups of Paquette[41] and Halterman[42] have prepared annulated verbenone and camphor derived compounds. Unlike the chiral monosubstituted cyclopentadienyl ligands where both faces of the ligand are rendered equivalent due to free rotation about the single σ-bond, the faces of the annulated cyclopentadienyl ligands can be homotopic, enantiotopic, or diastereotopic depending on the nature of the substitution.

2.0 RESULTS AND DISCUSSION

2.1 SYNTHESIS OF ANNULATED CHIRAL CYCLOPENTADIENE Zr-COMPLEXES

The first group of complexes tested were the annulated chiral cyclopentadiene Zr-complexes developed by Paquette et al. (Figure 5).[41] Originally designed for hydrogenation of alkenes,[43] structural studies of these complexes inspired their use in other stereoselective transformations.[44]

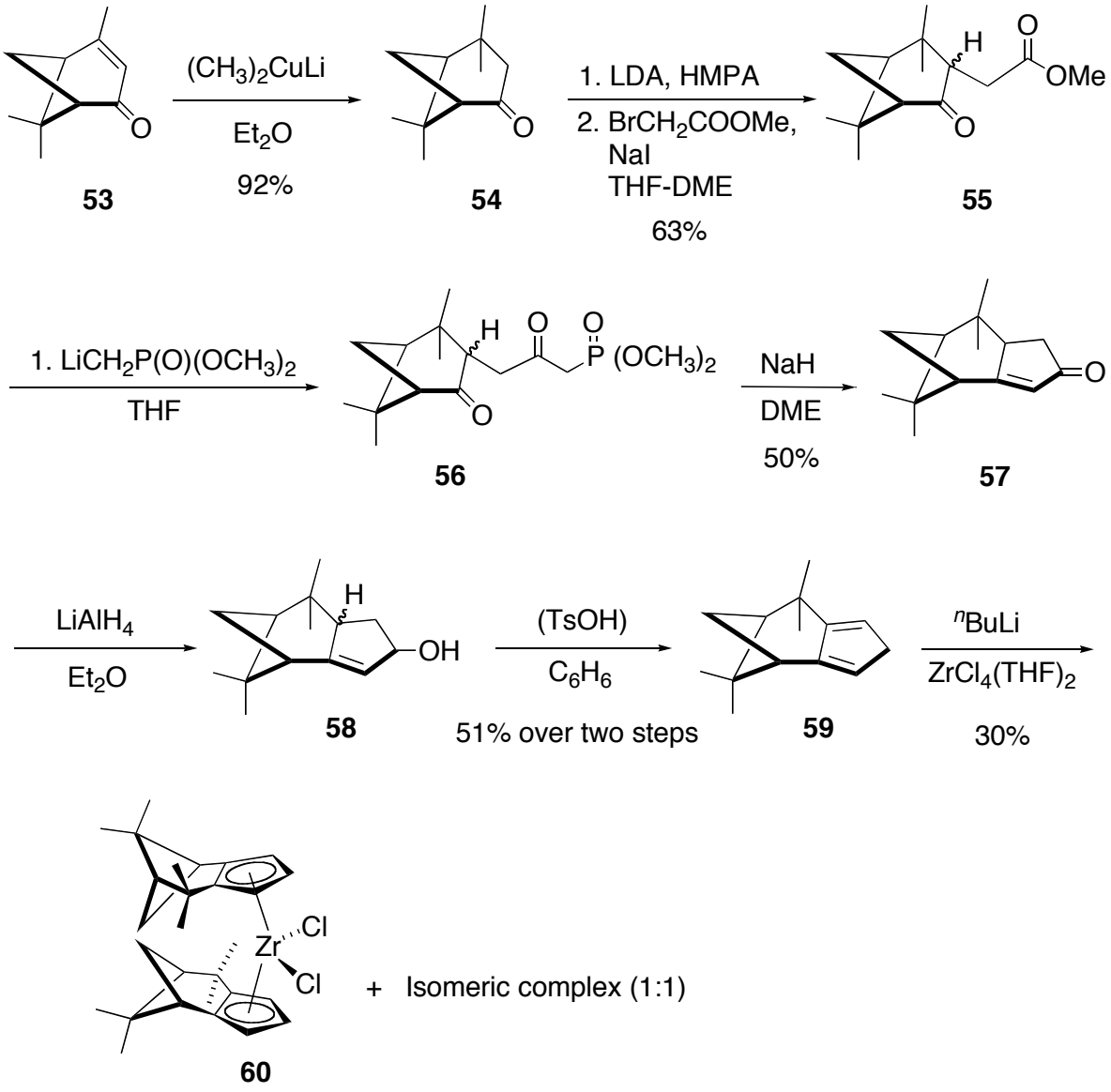


R = Me, ^{i}Pr, Ph

Figure 5. Annulated chiral cyclopentadiene Zr-complexes.

The synthesis of Zr-complex **60** began with the conjugate addition of lithium dimethylcuprate to the commercially available (1*S*)-(-)-verbenone **53**, affording **54** in 92% yield (Scheme 10). Alkylation of the lithium enolate of **54** with methyl bromoacetate provided **55**. According to Halterman and Vollhardt,[42] the ketone carbonyl function in **55** needed to be protected as the acetal before addition of the methyl phosphonate. Attempts to mask the ketone functionality as an acetal failed, possibly due to the steric

encumbrance at that position. This result was used in a direct conversion of keto ester **55** and the anion of dimethyl methylphosphonate to diketo phosphonate **56**.[41c] Subsequent deprotonation of intermediate **56** with sodium hydride in DME followed by heating for 18 h effected ring closure to cyclopentenone **57** in 50% yield. Diene **59** was obtained by reduction of **57** with $LiAlH_4$ in ether, followed by acid catalyzed dehydration. Attempted Isolation of alcohol **58** resulted in decomposition; therefore the dehydration used the crude material. Several attempts were made to form the Zr-complex **60** from diene **59**. Mostly, starting material was recovered. Different solvent systems and zirconium salts (i.e. $ZrCl_4$ or $ZrCl_4(THF)_2$) were tested. Diethyl ether and $ZrCl_4(THF)_2$ proved to be the best conditions for complex formation. Several trials only led to the isolation of a 1:1 mixture (^1H NMR) of **60** and an apparently C_1-symmetrical metallocene. No attempts were made to further purify this complex.[45]



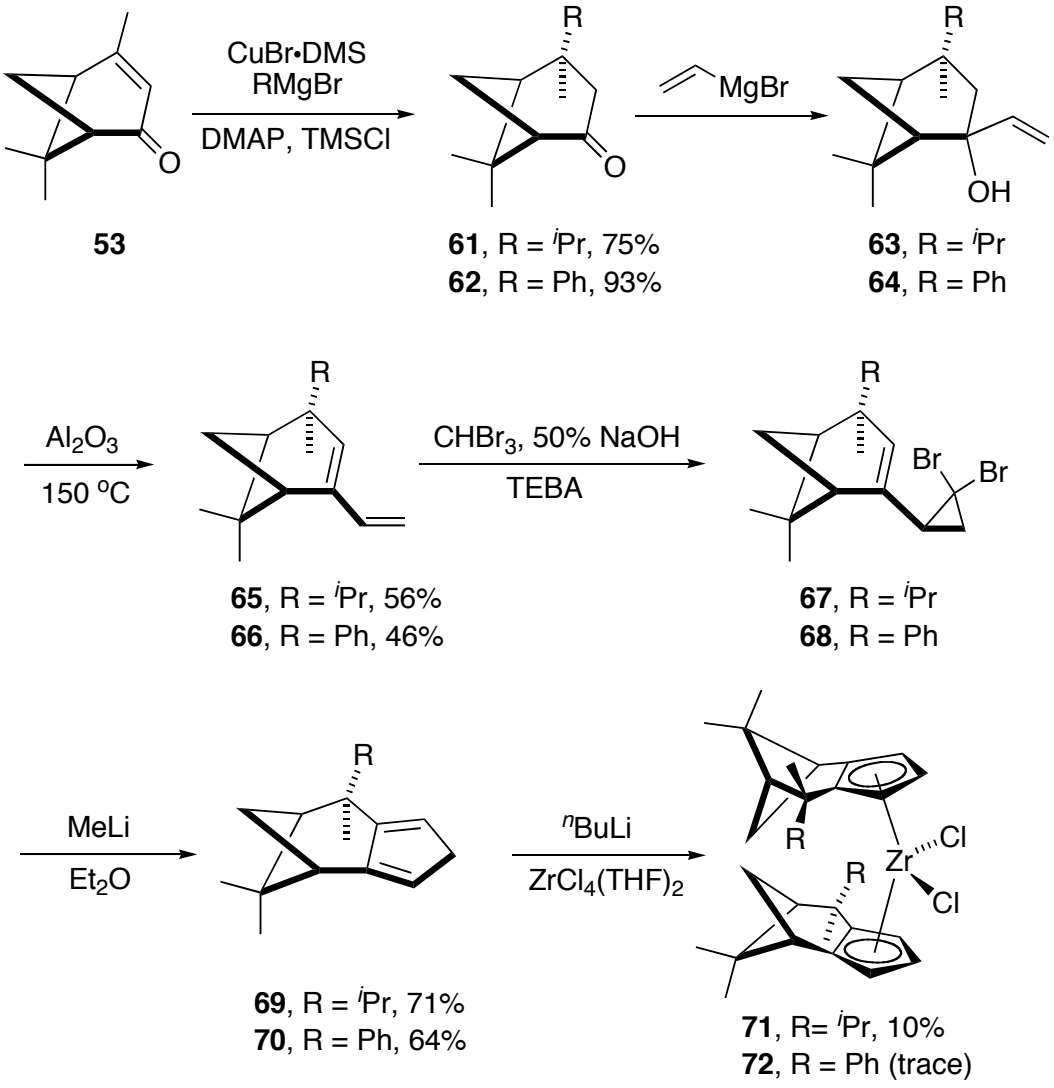
53 **54** **55** **56** **57** **58** **59** **60**

Scheme 10. Synthesis of verbenone-derived Zr-complex 60.

With little success in the isolation of pure **60**, we proceeded to prepare other analogs. Bulkier substituents such as *i*Pr- and Ph-were also explored by Paquette.[41c] Our first efforts to synthesize these analogs began by implementing the synthetic route in Scheme 10 (*vide supra*), starting with the conjugate addition of the corresponding lithium dialkylcuprate to ketone **53**, which yielded **61** in 75% yield and **62** in 93% yield,

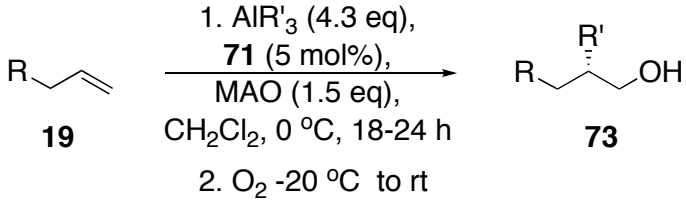
respectively. Subsequent alkylation with methyl bromoacetate failed in both cases, indicating severe steric encumbrance at the α-position of the carbonyl group.

Abandoning the unsuccessful approach, a procedure developed by Paquette[41a] to form similar analogues was utilized. Ketones **61** and **62** were treated with vinyl magnesium bromide at 0 °C. Addition occurred stereoselectively under steric control of the apical methyl group to give **63** and **64** (Scheme 11). Dehydration with activated basic Al_2O_3 yielded compounds **65** and **66** in 56% and 46% yield respectively. Both **67** and **68** underwent dibromocarbene addition to set the stage for a Skattebøl rearrangement for the purpose of annulating the cyclopentadiene ring onto the verbenone framework. Annulation occurred in 71% and 64% yield for isopropyl (**69**) and phenyl (**70**) cyclopentadienes, respectively. Subsequently, conditions to form the corresponding Zr-complexes were explored. Lithiation in a mixture of 2:1 hexanes/ Et_2O followed by treatment with $ZrCl_4(THF)_2$ were most suitable for the formation of metallocene **71**. Subjecting compound **70** to the same conditions only led to trace amounts of complex **72**.



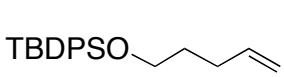
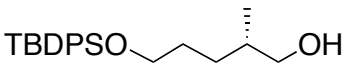
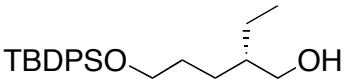
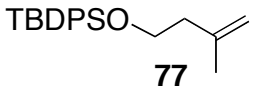
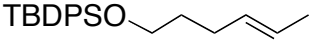
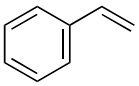
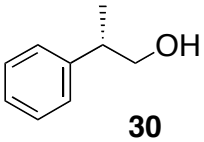
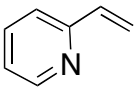
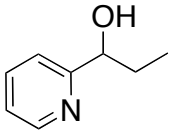
Scheme 11. Synthesis of ^{i}Pr- and Ph-analogs of 60.

With pre-catalyst **71** available for experimentation, we wanted to test its performance on the carboalumination of α-olefins. Using the protocol developed by Wipf and Ribe (*vide supra*),[14] 5 mol% of **71,** 4 equiv. of trialkylaluminum, and 1.5 equiv. of MAO in CH_2Cl_2 for 18-24 h (Equation 4) afforded the desired α-alkyl alcohols **73** in modest to good yields and low *ee* after oxidation (Table 3).



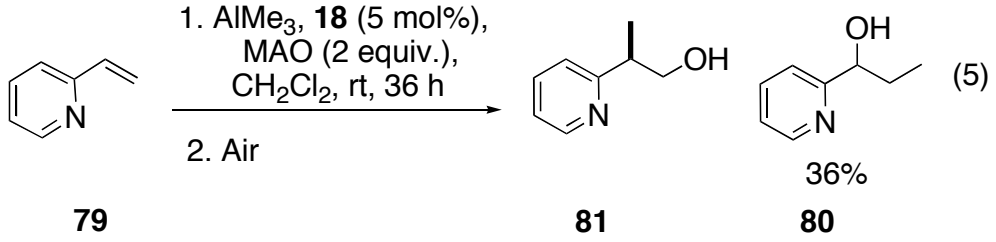
(4)

Table 3. Results of alkene carboaluminations with catalyst 71.[a]

Entry	Alkene	AlR_3	Product	Yield (%) [b]	ee (%)
1	 **74**	$AlMe_3$	 **75**	66	38[c]
2	**74**	$AlMe_3$	**75**	65	40[c,f]
3	**74**	$AlEt_3$	 **76**	40	34[c]
4	 **77**	$AlMe_3$	recovered SM (80%)		
5	 **78**	$AlMe_3$	recovered SM (97%)		
6	 **29**	$AlMe_3$	 **30**	54[g]	7[e]
7	 **79**	$AlMe_3$	 **80**	21[d]	

[a]Unless otherwise stated, the reaction was carried out at 0 °C in CH_2Cl_2 in the presence of **71** (5 mol%), AlR_3 (4.3 equiv) and MAO (1.5 equiv). [b]Isolated yields; [c]*ee* determined by chiral HPLC (Chiralcel OD); [d]yield determined after 24 h reaction time; [e]*ee* determined by Mosher ester analysis (^{1}H NMR); [f]carboalumination in the absence of MAO. [g]Absolute configuration determined by comparison of optical rotation with literature values.

In general, the chemical yields obtained with catalyst **71** where inferior to those reported by Wipf and Ribe using Erker's catalyst **18**.[14] α-Methyl alcohol **75** (Table 3, entry 1) was obtained in a modest 66% and a 38% *ee*. This same reaction performed in the absence of MAO led to similar results (entry 2). Ethylalumination of olefin **74** in the presence of complex **71** led to a 40% yield and a poor 34% *ee* (entry 3). Internal alkenes **77** and **78** did not undergo carboalumination (entries 4 and 5). Carbometalation of styrene **29** was sluggish and proceeded in only 54% yield and 7% *ee* (entry 6). Upon submitting 2-vinylpyridine to carbometalation in the presence of complex **71**, only regioisomer **80** was obtained in 21% yield (entry 7). It was previously noted by Wipf and Ribe[46] that carbometalation of 2-vinylpyridine **79** did not lead to the formation of the anticipated primary alcohol **81**. Instead, only the regioisomer **80** was formed and starting material **79** was recovered as the remainder of the mass balance (Equation 5). It was postulated that facial discrimination of the olefin occurred in the first step, but racemization during the oxidative cleavage of the organoalane intermediate, led to a racemic product.[46] This has been the first example of Zr-catalyzed carbometalation occurring with inverse regioselectivity.



(5)

79 **81** **80**

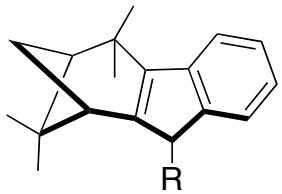
In light of these results, two conclusions were drawn. First, the bicyclic cyclopentadiene complex **71** was obviously inferior in terms of its asymmetric induction to the Erker catalyst **18**. Second, modest chemical yields and no β-hydride elimination were observed with **71**, thus it might be possible to tune the bicyclic complex class to increase the facial selectivity of the C-C bond forming step. Despite these promising results, the bicyclic cyclopentadiene complex remains inferior in terms of asymmetric

induction to Erker's complex **18**. Efforts to synthesize phenyl-derived complex **72** only lead to traces of desired product.

2.2 SYNTHESIS OF ANNULATED CHIRAL VERBENINDENES

The elucidation of ligand effects has been a central topic of research in the zirconocene-MAO catalyzed polymerization of α-olefins.[36b] Most investigations into ligand effects focus on the influence of the steric environment[47] and how electronic changes[48] in a ligand affect the metal center and its catalytic properties. Both effects have been invoked to explain the influence of different cyclopentadiene substituents on a metal during catalytic processes.[49]

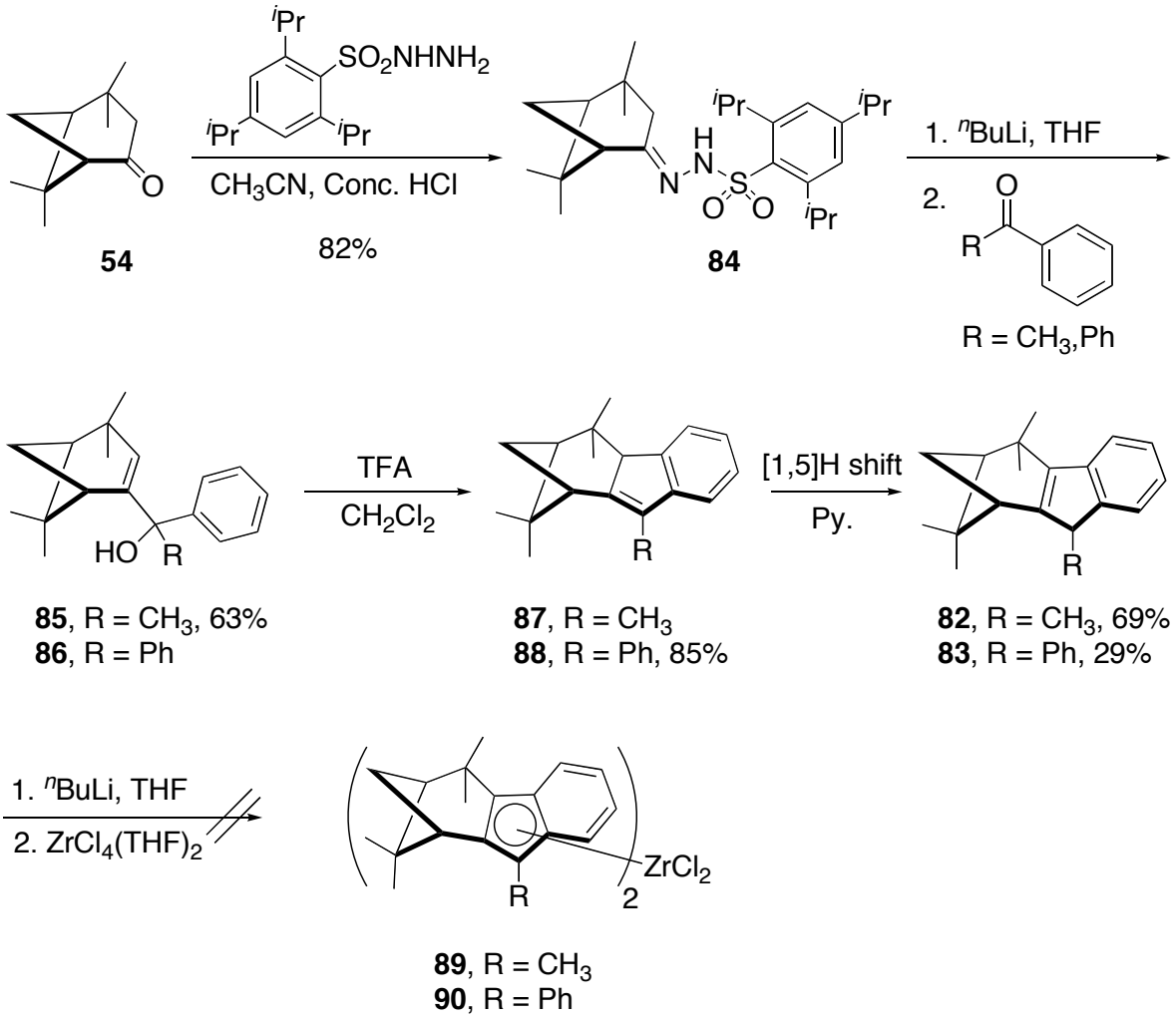
The verbenindenes provide a useful balance of steric and electronic effects that can be exploited in their use as transition metal ligands. First reported by Sowa et al.,[50] verbenindenes (Figure 6) are an extension of the annulated cyclopentadiene class and maintain the rigidity of the verbenone motif, but incorporate the indene moiety in a fused assembly. To our knowledge, Zr-complexes including this ligand type have not been synthesized, nor used in catalytic processes. Therefore, these ligands constitute suitable targets in our study of the Zr-catalyzed carboalumination of alkenes.



82, R = CH_3
83, R = Ph

Figure 6. Verbenone derived chiral annulated indenes.

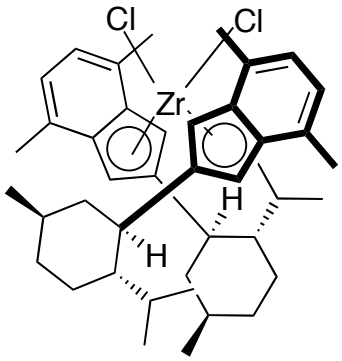
The synthesis of verbenindenes **82** and **83** began with a Shapiro lithiation followed by a Nazarov cyclization, converting ketone **54** to the corresponding trisyl hydrazone **84** in 82% yield (Scheme 12). Treatment of **84** with ^{n}BuLi, provided a vinyllithium intermediate that was quenched with an aryl ketone to afford allylic alcohols, **85** in 63% yield and **86** was used without further purification. To obtain the desired annulated indene, an acid-catalyzed electrocyclic reaction was used and provided **88** in 85% yield and **87** was used without further purification. Isomerization of indenes through successive [1,5]-hydrogen shift in pyridine led to the desired verbenindenes **82** and **83** in 69% and 29% yield, respectively. Indene **90** was obtained as a mixture of inseparable diastereomers and a *dr* of 1.8:1. Several trials to form the Zr-complex with either ligand resulted in recovered starting material. Deprotonation conditions were investigated by quenching the reaction with D_2O in intervals of 30 min, leading to deuterium incorporation (> 95%) at the 9-fluorene position after 4 h at -78 °C. From these results, we concluded that the verbenindene systems were too sterically encumbered to complex with the metal.



Scheme 12. Synthesis of verbenindenes and attempts of ligand complexation to zirconium.

2.3 SYNTHESIS OF BIS(2-MENTHYL-4,7-DIMETHYLINDENYL)ZIRCONIUM DICHLORIDE

Intrigued by the results obtained by Negishi with indene ligands, as well as the success in Zr-catalyzed carbomagnesations of alkenes with *ansa*-metallocenes[51] by Dzhemilev[52] and Hoveyda,[53] we set out to prepare Zr-complex **91** (Figure 7). Halterman et al. reported the preparation of **91** and its ability to polymerize propene in the presence of MAO and hydrogen.[54d] Incorporation of the methyl groups at the 4- and 7-position of the indene system on this complex provides a defined steric environment around the metal, when compared to Erker's catalyst **18** (Scheme 13).[54a-c] With this characteristic, as well as the chirality that the menthol auxilliary provides in complex **91**, it represented a suitable candidate for the catalyzed carboalumination.

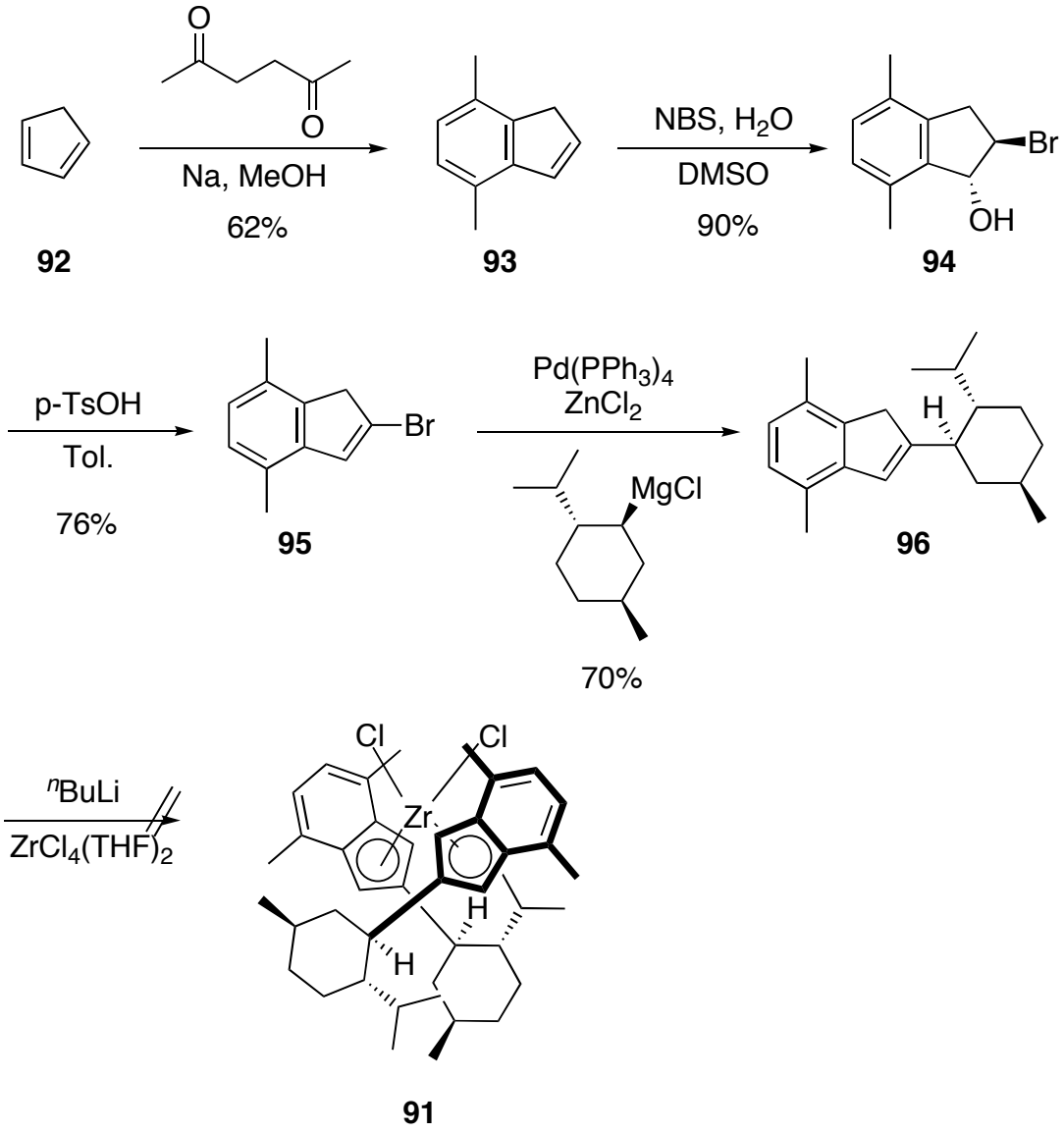


91

Figure 7. 2-Methyl-4,7-dimethylindenyl Zr-complex 91.

The expeditious synthesis of complex **91** began with the preparation of dimethylindene **93** from the condensation of cyclopentadiene **92** and 2,5-hexadione in the presence of sodium methoxide. Bromoindene **95** was obtained in 76% yield by bromohydration of cyclopentadiene with NBS in the presence of water followed by dehydration with TsOH. Coupling of bromoindene and menthylmagnesium chloride

under Negishi conditions afforded **96** in 70% yield with retention of configuration.[55] Several attempts to obtain Zr-complex **91** only lead to the recovery of starting material **96**.



Scheme 13. Synthesis of 2-methyl-4,7-dimethylindenyl Zr-complex 91.

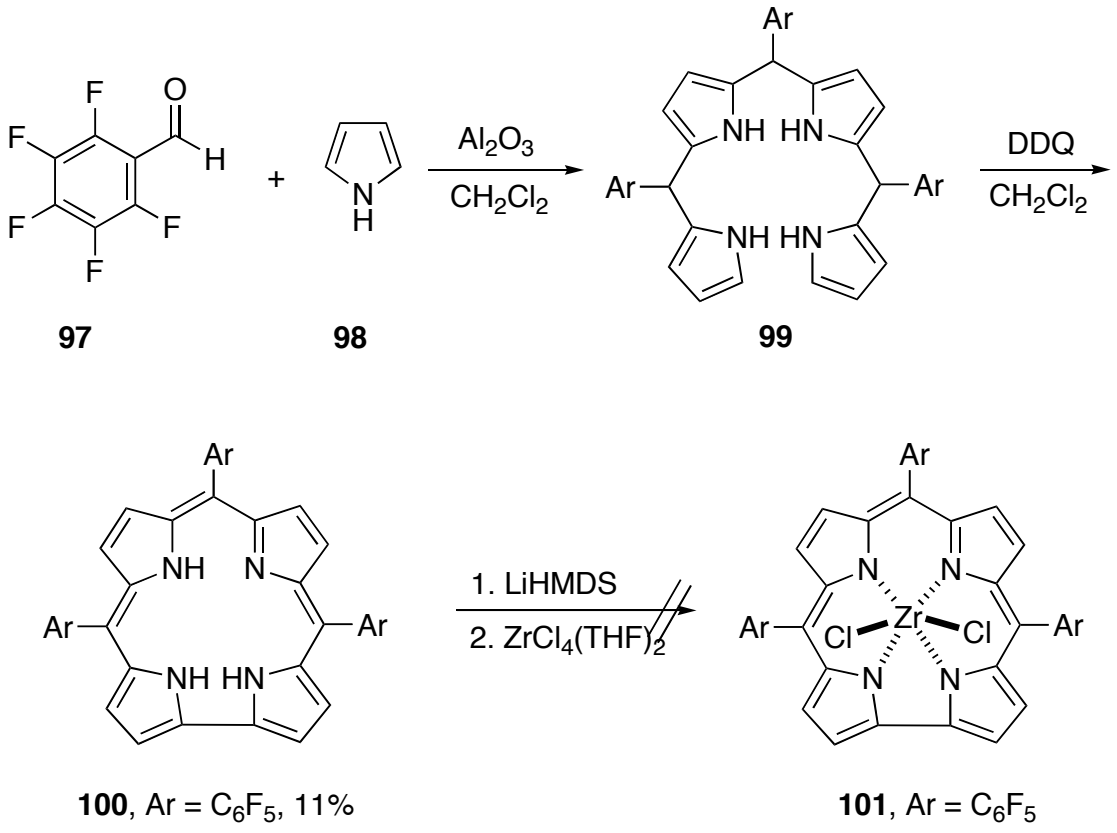
3.0 NON-METALLOCENE Zr-COMPLEXES

The field of metal-catalyzed polymerization has seen substantial growth in the development of a new generation of "non-metallocene" catalysts, mainly due to the promising results in the polymerization of ethylene to either linear or highly branched polyethylene (PE). Most studies have focused on group 4 transition metals and their derivatives as pre-catalysts. More recently, complexes containing non-cyclopentadienyl ligands have also been developed as homogeneous polymerization catalysts. Among them are complexes with ligands such as amidate,[56] amido,[57] oxazoline,[58] porphyrin,[59] alkoxy,[60] aryloxy,[61] and ketonate.[62] From this variety of complexes, group 4 metal complexes containing amide ligand systems have shown promising results for olefin polymerization. A formal lower electron count ($[R_2N)_2Zr]^+$ is a 10-electron species; compared with 14-electrons for $[Cp_2ZrR]^+$) is likely to afford a more electrophilic and potentially more active catalyst.[63]

3.1 SYNTHESIS OF CORROLE Zr-COMPLEXES

Corroles have emerged as a new class of ligands that have shown potential applications in areas such as materials, pharmaceutical agents, and catalysis.[64] Gross et al. disclosed a short synthetic sequence to form corroles.[65] Following this procedure, the synthesis of **100** began with the condensation of pyrrole with aldehyde **97**, followed by DDQ oxidation to form the desired product in a 11% yield (Scheme 14). Currently this

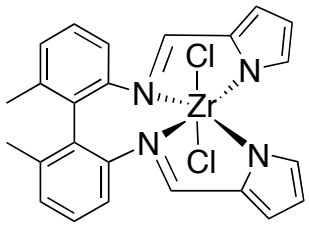
is the best method to synthesize corroles. The side products observed by NMR were the corresponding porphyrins, dimers, and tetramers. Efforts to complex corrole **100** with zirconium following the same procedure utilized for the porphyrins complexes lead only to recovery of the starting material. Using solvents such as THF, DME, or toluene or heating the reaction mixture did not improve these results. We surmised that the lack of complexation of Zr (IV) with the corrole N_4 could be a result of the inability of Zr (IV) (0.87 Å) to fit into the constrained corrole plane. This observation is in agreement with the corrole ligands' ability to complex to smaller metal ions such as Fe (IV) (0.72 Å) and Co (IV) (0.54 Å).[66]



Scheme 14. Attempted synthesis of corrole Zr-complex 101.

3.2 SYNTHESIS OF 6,6'-DIMETHYLBIANILINE-BASED ZIRCONIUM COMPLEXES

Other complexes containing ligands with N-donor atoms include amidinato,[67] diamido,[68] triamidoamine,[69] and diamido-diamine.[70] Among these classes of ligands, chiral zirconium complexes containing bidentate and tetradentate diamido ligands with aniline backbones have been prepared but not tested in the catalysis of discrete organic transformations. Some have been tested in the polymerization of alkenes.[71] Brintzinger reported the synthesis of the chiral 6,6'-dimethylbianiline-based zirconium complex **102** (Figure 8).[72] This complex showed modest activity in MAO-activated propene polymerization. We envisioned that a complex with these characteristics could also be utilized for the carboalumination of olefins.

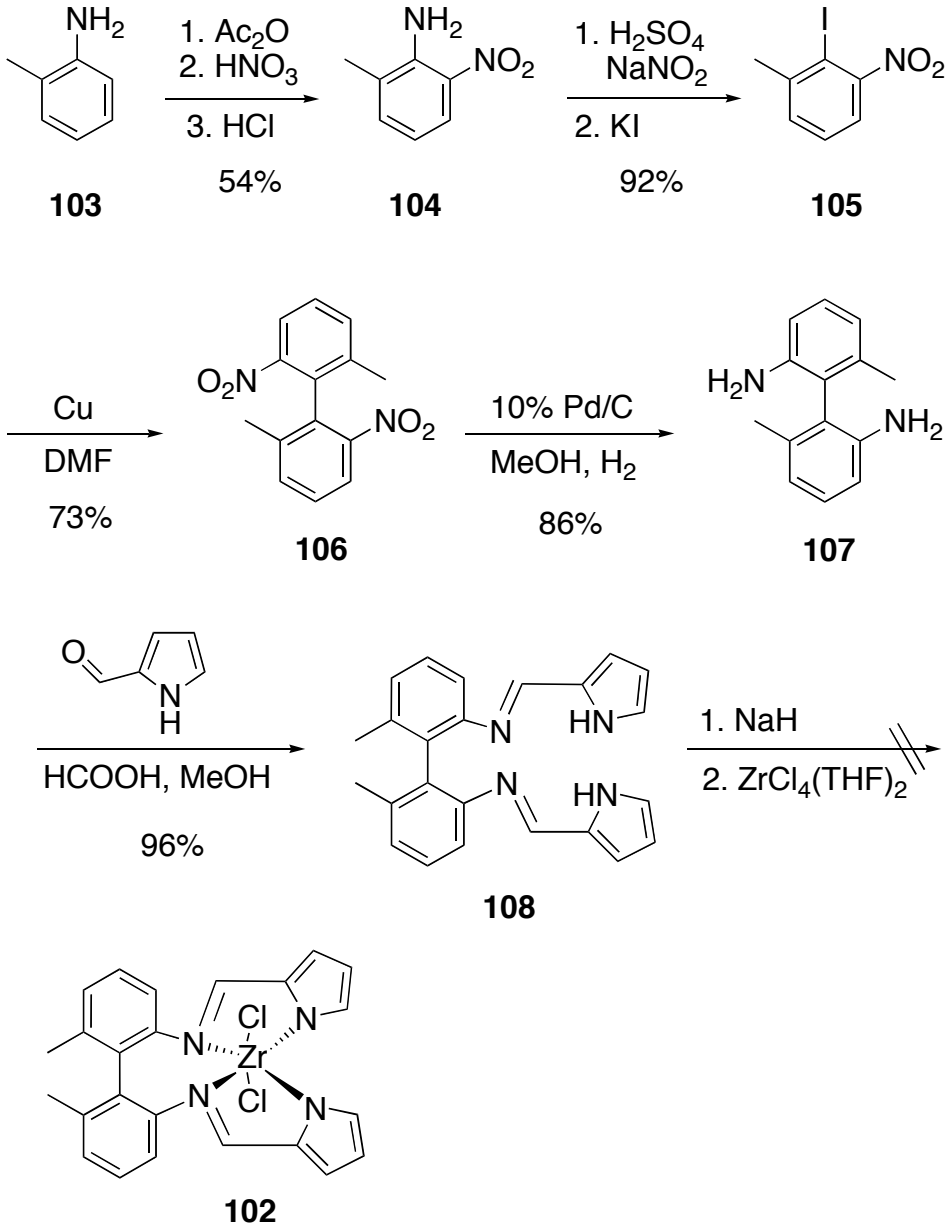


102

Figure 8. *N,N'*-(6,6'-Dimethylbiphenyl-2,2-diyl)diamine Zr-complex 102.

N,N'-(6,6'-Dimethylbiphenyl-2,2-diyl)diamine (AMB) **107** was prepared according to a literature procedure.[73] *o*-Toluidine **103** was nitrated with HNO_3 in the presence of acetic acid to give 2-amino-3-nitrotoluene **104** in 54% yield (Scheme 15). Iodination of nitrotoluene **105** was accomplished by diazotization of the aniline followed by treatment with KI to yield the desired product in 92% yield. Biaryl **106** was obtained by an Ullmann coupling in 73% yield. Nitro compound **106** was reduced by hydrogenation over palladium to obtain the ABM **107** in 86% yield. The dipyrrole diimine ligand **108** was readily prepared by condensation of **107** with pyrrole aldehyde in methanol. After a few

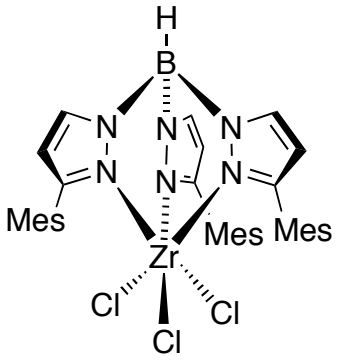
drops of formic acid were added as a catalyst, the product was isolated in 96% yield as a 1.28:1 mixture of inseparable distereomers. When deprotonation of the pyrroles of ligand **108** was attempted with NaH in THF, only starting material was recovered. After several attempts to form the complex, we abandoned this approach.



Scheme 15. Synthesis of dimethylbiphenyl bis (2-pyrrolemethyl)diimine 102.

3.3 SYNTHESIS OF ZIRCONIUM MONOANIONIC HYDRO(TRISPYRAZOLYL)BORATE COMPLEXES

Monoanionic hydro(trispyrazolyl)borate ligands are considered as formal analogues of cyclopentadiene in terms of donating six electrons to the metal center through their 6 σ-donor set, but they are more electron-donative and bulkier than a Cp ligand. They have been shown to have very high ethylene polymerization activities and compare favorably with Cp_2ZrCl_2 under similar conditions.[74] Jordan and Michiue reported an efficient synthesis of this class of compounds (Figure 9).[75] Additionally, Casagrande et al.[76] reported a high ethylene polymerization activity with complex **109a** in the presence of MAO. We wanted to test the activity of this novel complex in the Zr-catalyzed carboalumination of olefins.

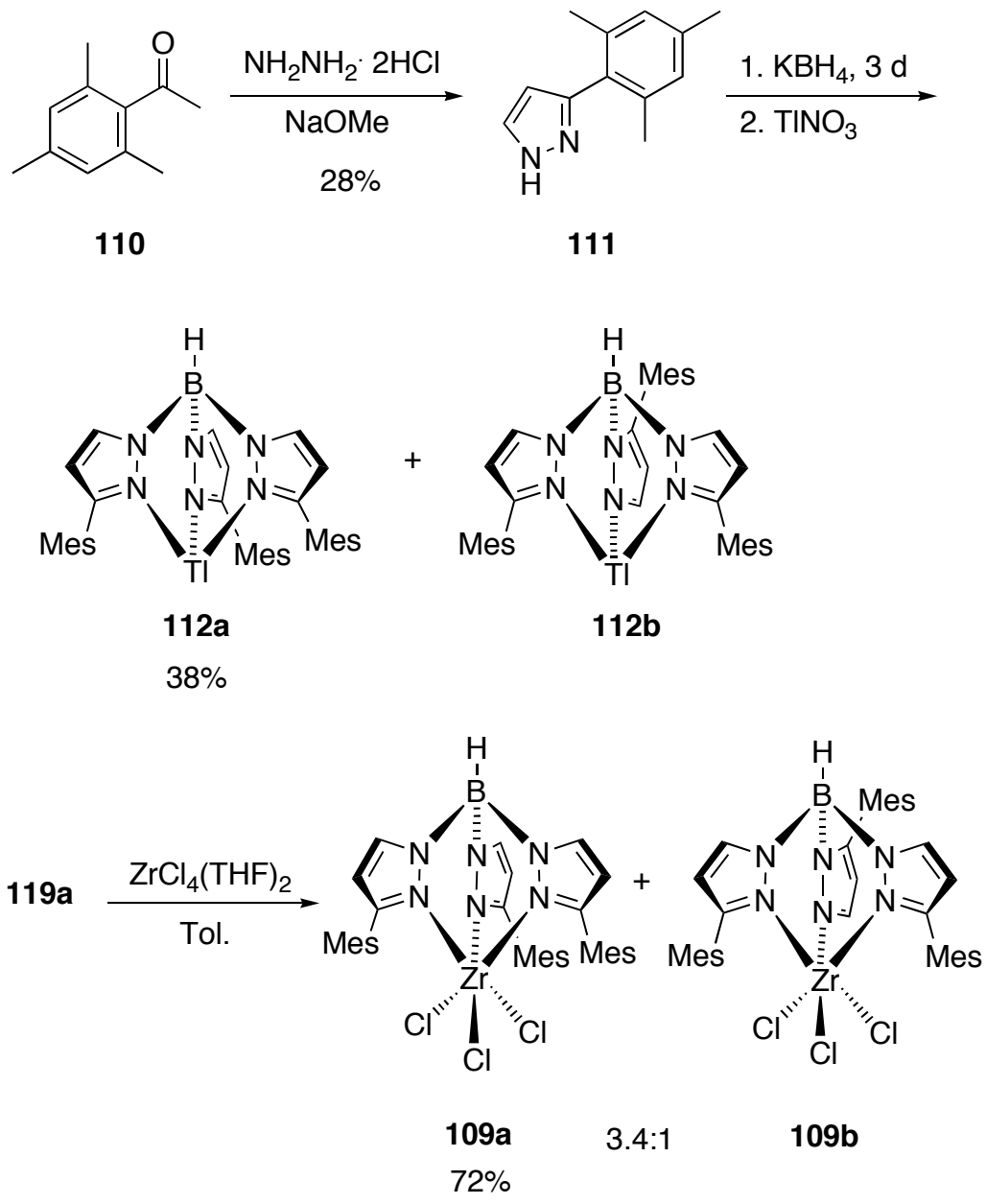


109a

Figure 9. Zirconium monoanionic hydro(trispyrazolyl)borate complex 109a.

The 3-mesitylpyrazole thallium complex ($Tp^{Ms}Tl$) **109a** was prepared from 2,4,6-trimethylacetophenone **110** via formylation with ethyl formate and treatment with hydrazine. Boron complexation of the mesityl group was achieved with potassium borohydride, followed by transmetalation to the thallium salts with $TlNO_3$ to give a 2:1 mixture of ligands **112a** and **112b**, respectively (Scheme 16).[77] Taking advantage of the

poor solubility of the minor product **112b**, pure ligand **112a** was obtained by crystallization from toluene. Upon treatment of ligand **112a** with $ZrCl_4(THF)_2$ in toluene, a 3.4:1 mixture of **109a** and **109b** was obtained with a 72% yield in favor of the desired product. Attempts to recrystallize the desired product from toluene only led the formation of the undesired regioisomer **109b**. We observed regioisomers due to a 1,2-borotropic shift. This indicated that the B-N bonds in these systems are labile and hence readily exchangeable with zirconium. With complex **109a** in hand,[78] we tested its performance to our standard carboalumination conditions. The reaction for either alkenes or alkynes did not proceed and only starting materials were recovered.

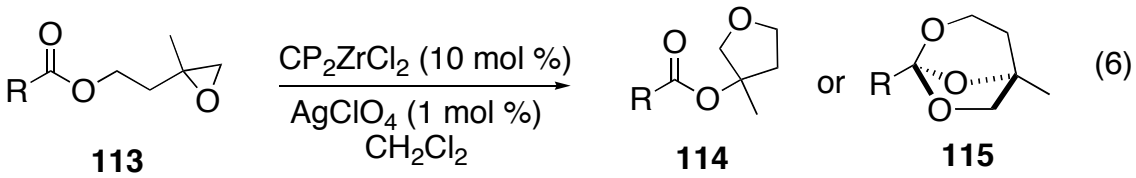


Scheme 16. Synthesis of Zr-hydro(trispyrazolyl)borate complexes.

Despite the little success obtained with Zr-complex **109a** in catalyzing the carboalumination reactions of alkenes, we wanted to further explore the reactivity of complex **109a** and its potential use in organozirconium chemistry. As part of our program to enhance the scope of organozirconium chemistry in organic synthesis, we have investigated cationic organozirconocene-induced epoxide ring-opening reactions.[79]

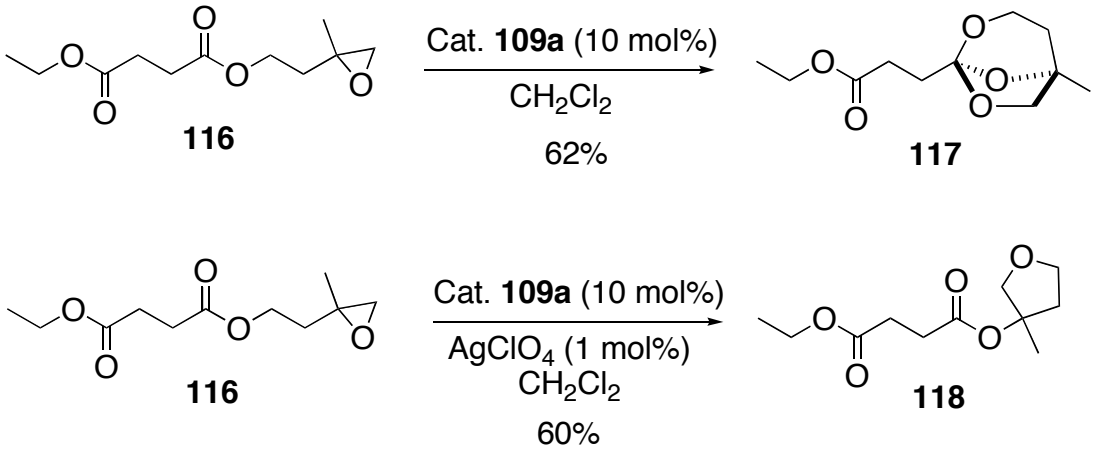
Since the 14-electron, cationic Cp_2ZrR^+ complex is more Lewis acidic than its neutral counterpart, this cationic species is expected to coordinate more readily to the oxygen and activate the epoxide to open new reaction pathways which are not possible with the neutral Cp_2ZrRCl species.

In prior studies, our group has found that the cationic zirconocene species prepared *in situ* from organozirconocene and catalytic amounts of $AgClO_4$ are efficient in initiating tandem epoxide rearrangement-aldehyde addition cascades and are compatible with a wide range of functional groups in the formation of dioxolanes, acyloxytetrahydrofurans and ortho esters from epoxy esters (Equation 6).[80]



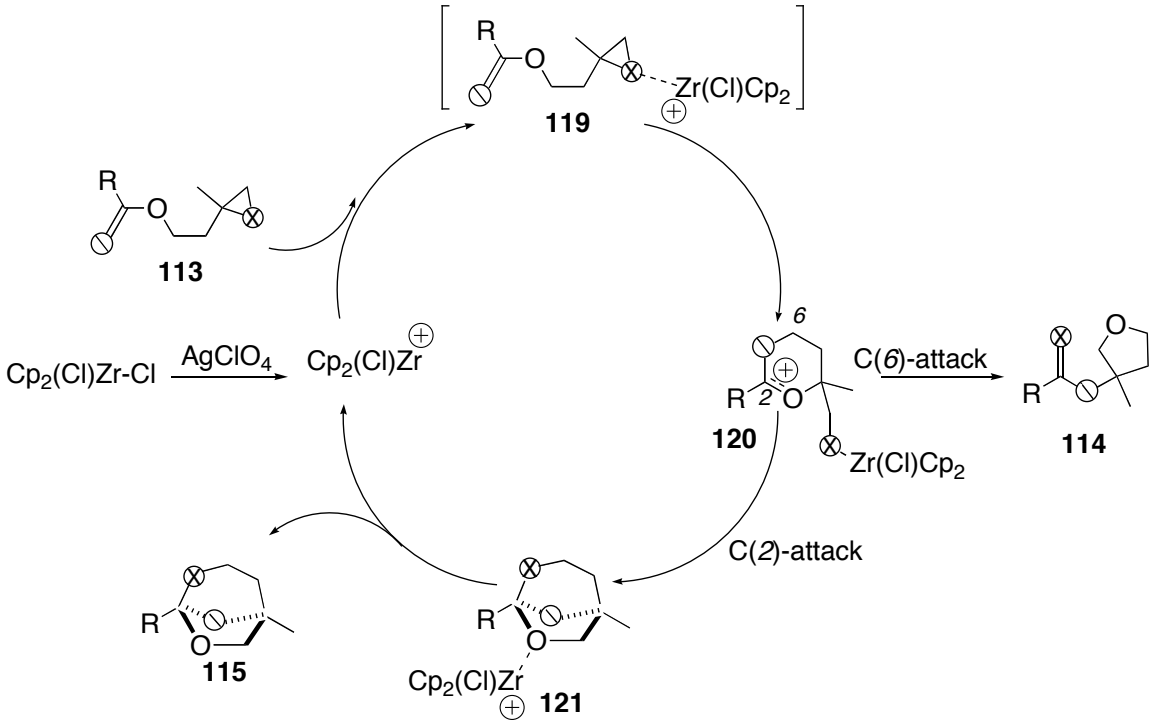
(6)

We wanted to investigate the reactivity of complex **109a** in this reaction. When epoxy ester **116**[80] was treated with Zr-complex **109a**, the ortho ester **117** was obtained in 62% yield (Scheme 17). The reaction required overnight stirring, and variations of temperature for increasing the rate of the reaction did not improve this process.



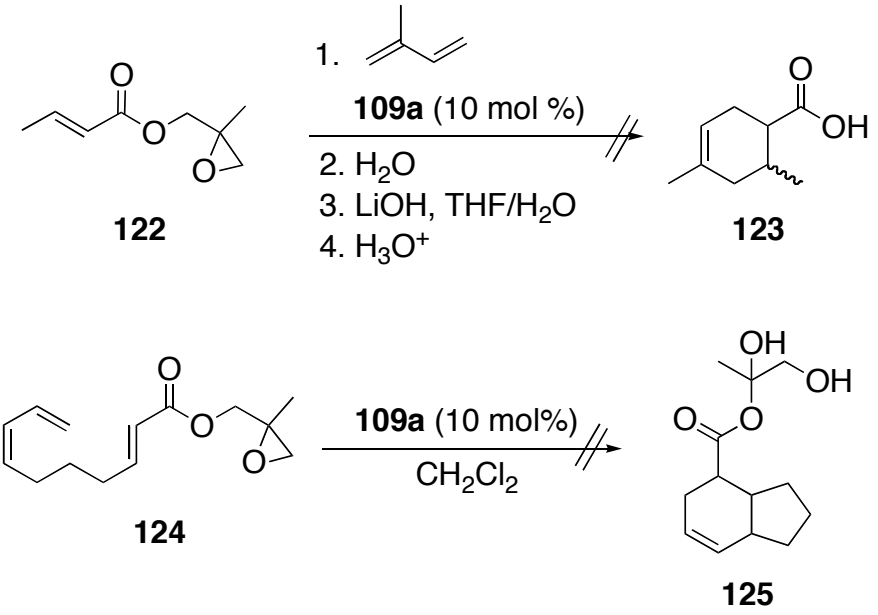
Scheme 17. Reactivity of Zr-complex 109a in the epoxy ester - ortho ester rearrangement.

Interestingly, the rearrangement with a catalytic amount of **109a** and 1 mol% of $AgClO_4$ did not lead to the corresponding ortho ester but provided tetrahydrofuran **118** in 60% yield. Presumably, as a consequence of the greater stability of the delocalized dialkoxycarbenium ion, **120** could be attacked at either the C(2)- or C(6)-position (Scheme 18).[79a,80] It has been postulated that the pathway for C(2)-attack required a lower activation energy and can be considered as the kinetically controlled route. The formation of the more stable rearranged furan **114** is a thermodynamically controlled pathway.[80]



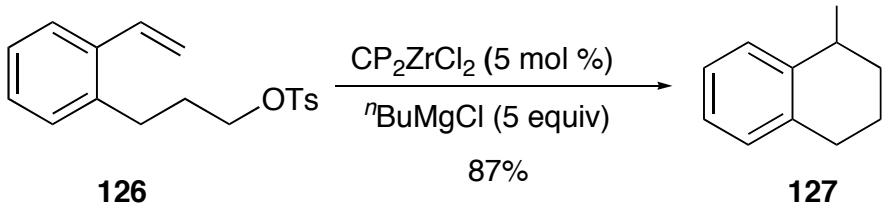
Scheme 18. Zirconocene-catalyzed epoxy ester- ortho ester rearrangement.

Having demonstrated that Zr-complex **109a** can act as a Lewis acid by promoting the epoxy ester- ortho ester rearrangement, we wanted to demonstrate the potential of complex **109a** in catalyzed cationic Diels-Alder reactions.[81] Wipf and Xu reported using catalytic amounts of Cp_2ZrCl_2 and $AgClO_4$ to promote cationic Diels-Alder reactions.[82] The generation of a highly electrophilic Diels-Alder dienophile is responsible for the reactivity of this process. When crotonate **122**[82] was treated with isoprene and catalytic amounts of Zr-complex **109a** in CH_2Cl_2, cyclo-adduct **123** was not obtained and only starting material was recovered in quantitative yield. Furthermore, when triene epoxy ester **124** was submitted to the same reaction conditions, no intramolecular product was obtained and only diol **125** was observed (Scheme 19). Currently, we have no explanation for the lack of reactivity of complex **109a** in this type of transformation.



Scheme 19. Attempted zirconocene-catalyzed inter- and intramolecular Diels-Alder reactions.

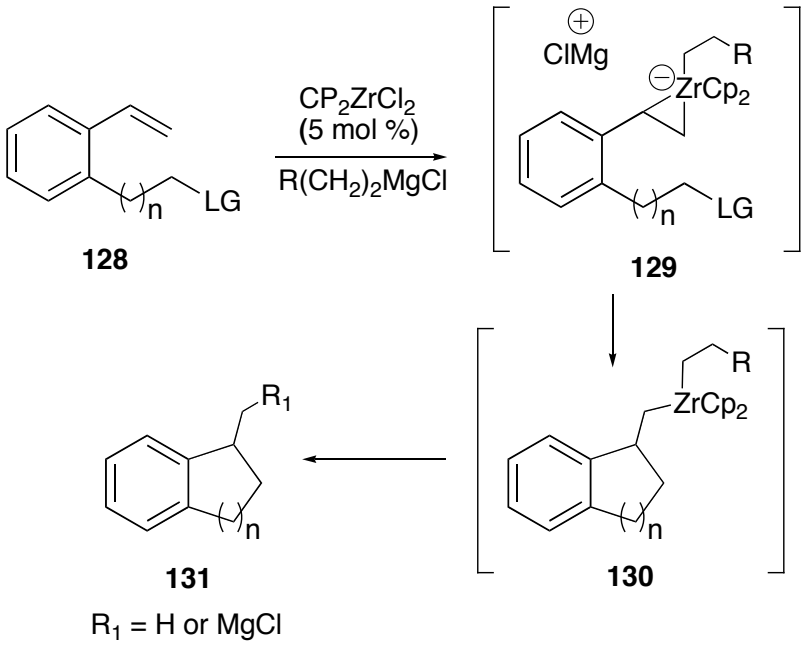
Hoveyda et al.[83] reported diastereoselective intramolecular Zr-catalyzed electrophilic olefin alkylations. These processes effect net coupling of an olefin and common electrophiles such alkyl halides and tosylates (Equation 7).



(7)

In these catalytic electrophilic alkylations, the C-C π system is rendered highly nucleophilic through association with the transition metal catalyst. It is the alkyl group of the electrophile that becomes incorporated within the product structure (vs. the alkyl group of the Grignard reagent); the role of the Grignard reagent is only to generate a potent nucleophile in the form of a reactive zirconate (cf. **129**, Scheme 20).[83] We wanted to determine the reactivity Zr-complex **109a** under these reaction conditions. However,

when tosylate **126** was treated with complex **109a** and ^{n}BuMgCl, substantial amounts of unidentified products were formed. It is not clear at this time what is responsible for the lack of product formation.



Scheme 20. Attempted Zr-catalyzed intramolecular electrophilic alkylation.

4.0 CONCLUSIONS

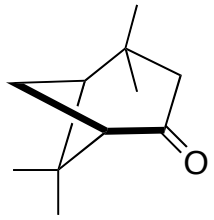
A series of zirconocene derivatives has been prepared and tested in the catalyzed carboalumination of alkenes. One of these complexes led to carboalumination in high chemical yield, but with inferior asymmetric induction when compared to Erker's catalyst. These results indicate that the electronic and steric features of a ligand can dramatically affect the properties of the zirconium catalyzed carboalumination process. Limitations of carboalumination processes are generally due to the lack of facial selectivity of the pre-catalyst upon binding to alkenes, and the possibility for alkene polymerization as a side reaction. Non-metallocene based Zr-complexes were studied and tested in cationic processes. The conversion of epoxy esters to ortho esters and tetrahydrofurans is catalytic in one of these non-metallocene complexes, which makes this process attractive for applications in organic synthesis.

5.0 EXPERIMENTAL PART

General Techniques. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions unless otherwise noted. Glassware was flame dried prior to use. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone ketyl. CH_2Cl_2 and toluene were obtained by passing through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H NMR) homogenous materials unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm E. Merck silica gel plates (60F-254) using 254 nm UV light as visualizing agent or by staining with an ethanolic solution of phosphomolybdic acid or *p*-anisaldehyde in ethanol/aqueous H_2SO_4 / CH_3CO_2H or Vaughn's reagent (aqueous solution of ammonium molybdate/ $CeSO_4$ / H_2SO_4) and heat as developing agents. Flash chromatography on Si_2O or basic Al_2O_3 was used to purify crude reaction mixtures.

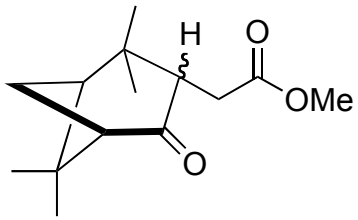
Melting points (Mp) are uncorrected and were recorded on a Laboratory Devices MeI-Temp II. Infrared spectra were determined on a Nicolet Avatar 360 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on either 300 MHz / 75 MHz (^1H / ^{13}C NMR) or 500 MHz / 125 MHz (^1H / ^{13}C NMR) using a Bruker AVANCE 300 MHz, Bruker QM-300 MHz or a Bruker DRX 500 MHz spectrometer and calibrated using residual undeuterated solvent as an internal reference. ^1H NMR are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), number of protons, and coupling constant(s). ^{13}C NMR spectra were obtained using the proton-decupled pulse sequence with a d_1 of 8 sec, and are tabulated by chemical shift. Chiral HPLC analysis was performed on a Dynamax SD-

200 delivery system in conjunction with a Dynamax UV-1 absorbance detector and a Chiracel OD column. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Mass spectrometry data was collected by the University of Pittsburgh's Department of Chemistry Mass Spectrometry Facility.



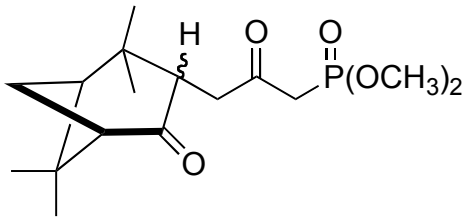
54

(1*S*,5*R*)-(-)-4,4,6,6-Tetramethylbicyclo[3.1.1]heptan-2-one (54).[41c] A solution of 25.3 g (133 mmol) of recrystallized CuI in 200 mL of Et_2O was cooled to 0 °C and 177 mL (1.5 M in ether, 266 mmol) of MeLi was introduced via cannula over 30 min. After 15 min, a solution of 20.0 g (133 mmol) of (1*S*,5*S*)-(-)-verbenone **53** and 33.8 mL (266 mmol) of TMSCl in 100 mL of Et_2O was added over 1 h. The reaction mixture was stirred at rt for 2 h before it was quenched by slow addition of 200 mL of sat. aq. NH_4Cl solution, and, after 2 h, 100 mL of conc. NH_4OH solution. The mixture was allowed to stir until the copper salts were dissolved. The Et_2O layer was washed with brine, dried (Na_2SO_4), filtered, concentrated and purified by chromatography on SiO_2 (R_f 0.5, EtOAc:hexanes, 1:9) to yield 20.4 g (123 mmol, 92%) of **54** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51-2.41 (m, 2 H), 2.35-2.25 (m, 2 H), 1.82 (app t, 1 H, J = 5.8 Hz), 1.57 (d, 1 H, J = 10.0 Hz), 1.30 (s, 3 H), 1.13 (s, 3 H), 1.02 (s, 3 H), 0.96 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.7, 58.6, 54.1, 48.7, 40.6, 32.5, 29.4, 27.6, 26.1, 25.8, 25.2; MS (EI) *m/z* (rel intensity) 166 (M^+, 30), 124 (50), 109 (65), 83 (100); HRMS (EI) calcd for $C_{11}H_{18}O$ 166.1358, found 166.1334.



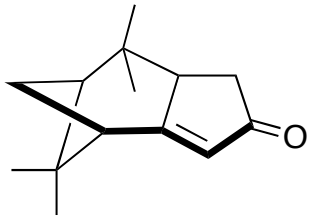
55

(1*S*,5*R*)-3-((Methoxycarbonyl)methyl)-4,4,6,6-tetramethylbicyclo[3.1.1] heptan-2-one (55).[41c] A solution of 10.1 mL (72.2 mmol) of isopropylamine in 20.0 mL of THF:DME (5:1) was cooled to -78 °C. After 15 min, 31.4 mL (2.3 M in hexanes, 72.2 mmol) of ^{n}BuLi was added dropwise and the resulting solution was allowed to stir for 2 h at -78 °C. A solution of 10.0 g (60.2 mmol) of **54** in 8.00 mL of DME was added over 30 min. The reaction mixture was allowed to stir for an additional 45 min, treated with 10.5 mL (60.2 mmol) of HMPA and allowed to stir for another 45 min at -78 °C. A solution of 11.4 mL (120 mmol) of methyl bromo acetate in 16.0 mL of DME and 18.4 g (120 mmol) of NaI were added rapidly and the mixture was allowed to stir for 1 h at -78 °C and at rt for 18 h before water was added. The aqueous layer was extracted with Et_2O (3x), and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered, concentrated, and purified by chromatography on SiO_2 (R_f 0.7, EtOAc:hexanes, 1:4) to yield 9.10 g (38.2 mmol, 63%) of **55** as a 1:1 mixture of inseparable diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.69 (s, 3 H), 2.96 (dd, 1 H, J = 8.6, 5.1 Hz), 2.73 (dd, 0.5 H, J = 15.9, 8.7 Hz), 2.68 (dd, 0.5 H, J = 15.9, 8.6 Hz), 2.53 (t, 1 H, J = 5.1 Hz), 2.49-2.39 (m, 1 H), 2.26 (dd, 0.5 H, J = 5.2 Hz), 2.20 (dd, 0.5 H, J = 5.2 Hz), 1.90 (t, 1 H, J = 6.0 Hz), 1.82 (d, 1 H, J = 10.8 Hz), 1.31 (s, 3 H), 1.11 (s, 3 H), 1.00 (s, 3 H), 0.82 (s, 3 H); MS (EI) *m/z* (rel intensity) 204 (M^+, 10), 136 (45), 97 (100), 69 (80); HRMS (EI) calcd for $C_{18}H_{22}O_3$ 238.1569, found 238.1558.



56

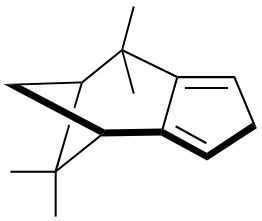
(1*S*,5*R*)-3-(3-(Dimethylphosphono)-2-oxoprop-1-yl)-4,4,6,6-tetramethyl bicyclo [3.1.1]heptan-2-one (56).[41c] A solution of 5.18 mL (48.5 mmol) of dimethyl methylphosphonate in 10.0 mL of THF was cooled to -78 °C. After 15 min, 22.1 mL (2.3 M in hexanes, 50.9 mmol) of ^{n}BuLi was added dropwise and the reaction mixture was stirred for 2 h at -78 °C. A solution of 5.77 g (24.2 mmol) of **55** in 50.0 mL of THF was added over 30 min at -78 °C. The reaction mixture was stirred at rt for 3 h before being quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3x), and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The resulting crude yellow oil was used directly in the next step.



57

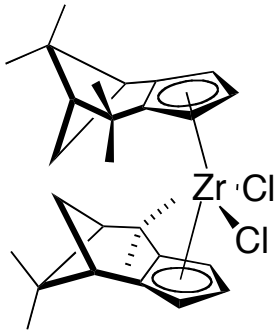
(1*S*,8*R*)-7,7,9,9-Tetramethyltricyclo[6.1.1.0]dec-2-en-4-one (57).[41c] A solution of 4.40 g (13.3 mmol) of **56** in 20.0 mL of DME was added dropwise to a slurry of 533 mg (60% in mineral oil, 13.3 mmol) of sodium hydride in 150 mL of DME at rt. The reaction mixture was heated to reflux for 2 h, cooled to rt, and quenched with water. The aqueous layer was extracted with Et_2O (3x). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. The resulting oil was purified by chromatography on SiO_2 (R_f 0.5, EtOAc:hexanes, 1:9) to give 1.35 g (6.65 mmol, 50%) of **57** as a single

distereomer and as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (d, 1 H, *J* = 2.5 Hz), 3.49-3.41 (m, 1 H), 3.08 (app t, 1 H, *J* = 5.5 Hz), 2.70 (dd, 1 H, *J* = 10.6, 6.1 Hz), 2.48 (dd, 1 H, *J* = 17.2, 6.4 Hz), 2.33 (dd, 1 H, *J* = 17.2, 4.8 Hz), 1.87 (app t, 1 H, *J* = 5.5 Hz), 1.49 (s, 3 H), 1.23 (s, 3 H), 1.18 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.5, 191.0, 123.3, 56.3, 49.2, 47.3, 40.8, 39.1, 36.7, 34.2, 29.8, 28.5, 25.8, 25.2; MS (EI) *m/z* (rel intensity) 204 (M^+, 10), 136 (45), 97 (100), 69 (80).



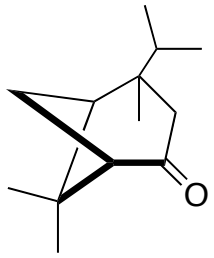
59

(1*S*,8*R*)-7,7,9,9-Tetramethyltricyclo[6.1.1.0]deca-2,5-diene (59).[41c] To a solution of 225 mg (5.94 mmol) of $LiAlH_4$ in 24.0 mL of Et_2O was added a solution of 1.21 g (5.94 mmol) of **57** in 8.00 mL of Et_2O over 30 min at rt. After 5 min, the reaction mixture was cooled to 0 °C, quenched with H_2O and treated with 1 N HCl solution. The aqueous phase was extracted with Et_2O (4x) and the combined organic layers were concentrated. A solution of the resulting colorless oil in 10.0 mL of benzene was treated with 113 mg (0.594 mmol) of TsOH and stirred for 18 h. After addition of K_2CO_3 and $MgSO_4$ the solution was allowed to stand for 2 h with intermittent swirling, filtered and evaporated. The residual oil was purified by chromatography on Al_2O_3 (R_f 0.9, pentane) to yield 570 mg (3.03 mmol, 51%) of **59** as a yellow oil: $[\alpha]_D$ + 31.6 (*c* 6.0, hexanes, 24 °C); ^{1}H NMR (300 MHz, C_6D_6) δ 6.00 (bs, 1 H), 5.80 (bd, 1 H, *J* = 1.4 Hz), 2.89 (bs, 2 H), 2.66 (app t, 1 H, *J* = 5.2 Hz), 2.38 (dt, 1 H, *J* = 10.8 Hz, 5.9 Hz), 1.60 (app t, 1 H, *J* = 5.7 Hz), 1.49 (d, 1 H, *J* = 10.1 Hz), 1.32 (s, 3 H), 1.25 (s, 3 H), 1.19 (s, 3 H), 0.89 (s, 3 H).



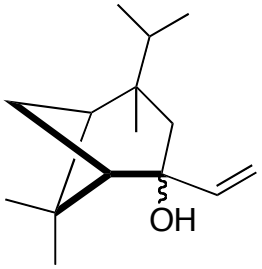
60

Bis(η^5-(1*S*,8*R*)-7,7,9,9-Tetramethyltricyclo{6.1.1.0]deca-3,5-dien-2-yl) dichlorozirconium (60).[41c] To a solution containing 200 mg (1.06 mmol) of **59** in 8.00 mL of Et_2O, 0.79 mL (1.4 M in hexanes, 1.12 mmol) of ^{n}BuLi was added at -78 °C. The reaction mixture was stirred for 15 min at -78 °C and an additional 15 min at rt. Upon cooling the reaction mixture to -78 °C, 200 mg (0.530 mmol) of $ZrCl_4(THF)_2$ was added in one portion. After stirring the reaction mixture for 30 min at -78 °C and 18 h at rt, volatiles were removed under vacuum. The crude mixture was redissolved in $CHCl_3$, treated with 1 N HCl solution and extracted with $CHCl_3$ (3x). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Recrystallization from EtOH at -20 °C gave 246 mg (0.318 mmol, 30%) of **60** as yellow needles and as a 1:1 mixture of inseparable complex isomers: $[\alpha]_D$ 258 (*c* 0.2, toluene, 24 °C); Mp 200.1 - 203.7 °C (EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (b, 1 H), 6.28 (app t, 1 H, *J* = 2.8 Hz), 6.21 (b, 1 H), 6.14 (app t, 1 H, *J* = 2.7 Hz), 5.95 (app t, 1 H, *J* = 2.2 Hz), 5.88 (app t, 1 H, *J* = 2.2 Hz), 2.77 (app t, 2 H, *J* = 4.5 Hz), 2.62-2.53 (m, 2 H), 2.08 (dd, 2 H, *J* = 1.05, 6.2 Hz), 1.69 (app t, 1 H, *J* = 6.0 Hz), 1.42 (s, 3 H), 1.40 (s, 3 H), 1.39 (s, 6 H), 1.28 (s, 3 H), 1.27 (s, 3 H), 0.41 (s, 3 H), 0.41 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.7, 146.2, 137.5, 136.7, 113.5, 113.1, 113.0, 112.5, 109.5, 107.7, 54.5, 45.3, 44.5 (2 C), 39.8, 39.6, 31.6, 31.4, 30.8, 29.9, 29.8, 27.6, 24.3; MS (EI) *m/z* (rel intensity) 534 (M^+, 30), 498 (15), 349 (100); HRMS (EI) calcd for $C_{28}H_{38}Cl_2Zr$ 534.1398, found 534.1388.



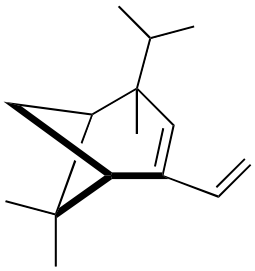
61

General Protocol A. (1*R*)-4-Isopropyl-4,6,6-trimethylbicyclo[3.1.1]hept-3-en-2-one (61).[41a] A solution containing 0.547 g (2.66 mmol) of CuBr•DMS and 13.0 g (106 mmol) of DMAP in 100 mL of THF was treated with 53.2 mL (2.0 M in ether, 106 mmol) of isopropylmagnesium chloride dropwise at -78 °C. After 15 min, a solution of 8.00 g (53.2 mmol) of (1*S*,5*S*)-(-)-verbenone **53** and 13.5 mL (106 mmol) of TMSCl in 75.0 mL of THF was added over 1 h. The reaction mixture was stirred at rt for 2 h before it was quenched by slow addition of sat. aq. NH_4Cl solution, and, 2 h later, conc. NH_4OH solution. The mixture was allowed to stir until the copper salts were dissolved. The aqueous layer was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated, and purified by chromatography on SiO_2 (R_f 0.6, EtOAc:hexanes, 1:9) to yield 7.74 g (25.0 mmol, 75%) of **61** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48 (dd, 1 H, J = 10.3, 5.3 Hz), 2.42-2.36 (m, 1 H), 2.22 (d, 1 H, J = 19.6 Hz), 2.09 (app t, 1 H, J = 5.1 Hz), 1.73 (sept, 1 H, J = 6.8 Hz), 1.63 (d, 1 H, J = 10.8 Hz), 1.34 (s, 3 H), 0.99 (s, 3 H), 0.93 (s, 3 H), 0.84 (d, 3 H, J = 6.7 Hz), 0.71 (d, 3 H, J = 6.7 Hz); MS (EI) *m/z* (rel intensity) 195 ($[M+1]^+$, 5), 194 (M^+, 30), 151 (40), 109 (70), 83 (100).



63

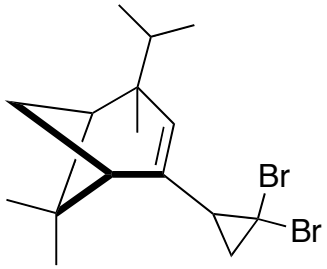
(1*R*,4*R*)-4-Isopropyl-4,6,6-trimethyl-2-vinylbicyclo[3.1.1]heptan-2-ol (63).[41a] A solution containing 15.0 mL (1.0 M in THF, 15.0 mmol) of vinylmagnesium bromide in 5.00 mL of THF was treated with a solution of 1.94 g (10.0 mmol) of **61** in 10.0 mL of THF at 0 °C. The reaction mixture was allowed to stir at 0 °C for 2 h and at rt for an additional 6 h prior to quenching with sat. aq. NH_4Cl. The aqueous phase was extracted with Et_2O (2x). The combined Et_2O layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The resulting crude oil was used directly for the next step.



65

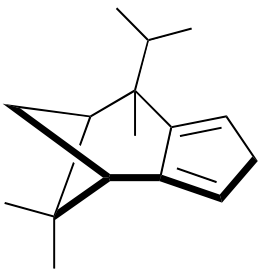
(1*R*,4*S*)-4-Isopropyl-4,6,6-trimethyl-2-vinylbicyclo[3.1.1]hept-2-ene (65).[41a] To 100 g of basic alumina (activity I, activated at 450 °C for 18 h) was added, 1.00 g (4.50 mmol) of **63**. This evenly coated paste was allowed to stand for 4 h at rt followed by Kugelrohr distillation (165 °C, 1.5 mmHg, 2 h). The crude oil was purified by chromatography on SiO_2 (R_f 0.8, hexanes) to yield 511 mg (2.50 mmol, 56%) of **65** as a yellow oil: ^{1}H NMR (300 MHz, C_6D_6) δ 6.41 (dd, 1 H, J = 17.4, 10.7 Hz), 5.56 (br s, 1 H), 5.12 (d, 1 H, J = 16.8 Hz), 4.93 (d, 1 H, J = 10.7 Hz), 2.56 (app t, 1 H, J = 5.4 Hz), 2.28-2.17 (m, 1 H), 1.99-1.93 (m, 1 H), 1.75 (sept, 1 H, J = 6.8 Hz), 1.46 (d, 1 H, J = 9.3 Hz),

1.31 (s, 3 H), 0.99 (s, 3 H), 0.86 (s, 3 H), 0.85 (d, 3 H, J = 6.8 Hz), 0.67 (d, 3 H, J = 6.9 Hz); MS (EI) *m/z* (rel intensity) 204 (M^+, 10), 161 (40), 119 (100), 105 (55), 91 (50); HRMS (EI) calcd for $C_{15}H_{24}$ 204.1878, found 204.1868.



67

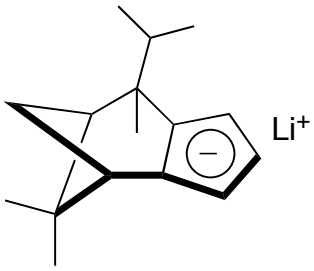
(1*R*,4*S*)-2-(2,2-Dibromocyclopropyl)-4-isopropyl-4,6,6-trimethylbicyclo[3.1.1] hept-2-ene (67).[41a] To a solution of 500 mg (2.45 mmol) of **65** in 15.0 mL of CH_2Cl_2 was added 1.24 mL (4.90 mmol) of bromoform, 12.0 mg (53.0 μmol) of TEBA and 2 drops of ethanol. The mixture was vigorously stirred at 0 °C while 1.30 mL (24.5 mmol) of a 50% aq. NaOH solution was added slowly. Stirring was continued for an additional 24 h at rt before water was added. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to yield a yellow oil which was used in the next step without further purification. Diagnostic shift in ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (bs, 1 H).



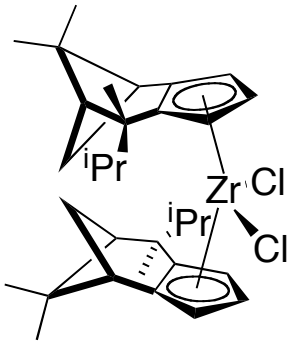
69

(1*S*,7*S*,8*S*)-7-Isopropyl-7,9,9-trimethyltricyclo-[6.1.1]deca-2,5-diene (69).[41a] A solution containing 3.16 g (8.40 mmol) of dibromide **67** in 330 mL of Et_2O was treated

with 24.0 mL (1.4 M in ether, 33.6 mmol) of methyllithium at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 24 h before it was added to a water-ice mixture. The aqueous layer was extracted with 100 mL of Et_2O (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated, and purified by chromatography on SiO_2 (R_f 0.7, pentane) to yield 1.29 g (5.96 mmol, 71%) of **69** as a colorless oil: $[\alpha]_D$ -7.3 (*c* 1.0, hexanes, 24 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09 (bs, 1 H), 5.76 (bs, 1 H), 2.96 (AB, q, 2 H, *J* = 23.7 Hz), 2.63 (app t, 1 H, *J* = 5.2 Hz), 2.41 (app pent, 1 H, *J* = 6.0 Hz), 1.94 (app t, 1 H, *J* = 6.0 Hz), 1.90-1.75 (m, 1 H, 6.9 Hz), 1.54 (d, 1 H, *J* = 10.2 Hz), 1.36 (s, 3 H), 1.06 (s, 3 H), 1.04 (d, 3 H, *J* = 6.9 Hz), 0.76 (d, 3 H, *J* = 6.7 Hz), 0.75 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 151.9, 125.4, 119.3, 51.2, 43.7, 42.4, 41.5, 40.3, 34.0, 28.0, 27.7, 24.4, 18.5, 18.1, 16.8.



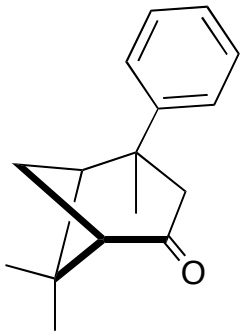
71a



71

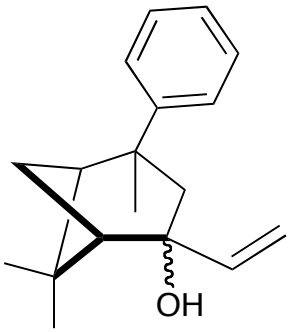
(+)-Bis[η^5-(1*R*,7*R*,8*R*)-7-isopropyl-7,9,9-trimethyl-tricyclo[6.1.1.0]deca-2,5-dien-4-dichlorozirconium (71).[41a-c] To a solution containing 0.390 g (1.80 mmol) of **69** in 12.0 mL of hexanes and 5.00 mL of Et_2O was added 0.943 mL (2.1M in hexanes, 1.98 mmol) of ^{n}BuLi dropwise at 0 °C while a white solid precipitated. The reaction mixture was stirred at 0 °C for 1 h and at rt for 24 h. Removal of the volatiles under vacuum left **71a** as a yellow solid which was treated with 340 mg (0.900 mmol) of $ZrCl_4(THF)_2$ The mixture was cooled to -78 °C, 8.00 mL of CH_2Cl_2 was added slowly, and the yellow slurry was allowed to stir for 1 h at -78 °C before being warmed to rt and stirred overnight. The reaction mixture was filtered through Celite and concentrated *in*

vacuo. The crude solid was dissolved in 5.00 mL of dry toluene and cooled to -20 °C. The resulting crystals were washed with pentane to give 109 mg (0.185 mmol, 10%) of **71** as yellow crystals: Mp 189.6-193.2 °C (pentane); $[\alpha]_D$ 117.1 (*c* 0.1 $CHCl_3$, 24 °C); ^1H NMR (500 MHz, $CDCl_3$) δ 6.26 (app t, 2 H, *J* = 2.5 Hz), 6.22 (app t, 2 H, *J* = 2.9 Hz), 5.88 (app t, 2 H, *J* = 2.5 Hz), 2.76 (app t, 2 H, *J* = 5.1 Hz), 2.61 (sept, 2 H, *J* = 6.7 Hz), 2.51-2.43 (m, 2 H), 2.34 (app t, 2 H, *J* = 10.4 Hz), 2.00 (app t, 2 H, *J* = 5.4 Hz), 1.40 (s, 6 H), 1.07 (d, 6 H, *J* = 6.6 Hz), 1.01 (s, 6 H), 0.76 (d, 6 H, *J* = 6.8 Hz), 0.39 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 141.2, 116.7, 111.7, 109.6, 51.5, 45.8, 45.4, 44.1, 32.2, 28.6, 27.9, 24.6, 19.9, 19.5, 16.8 ppm; MS (EI) *m/z* (rel intensity) 590 (M^+, 30), 549 (40), 377 (100), 131 (60); HRMS (EI) calcd for $C_{32}H_{46}Cl_2Zr$ 590.2024, found 590.1984.



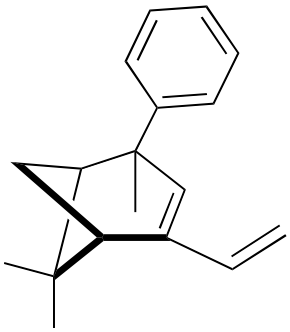
62

(1*R*)-4,6,6-Trimethyl-4-phenylbicyclo[3.1.1]hept-2-one (62).[41a] According to General Protocol A, 0.582 g (2.83 mmol) of CuBr•DMS, 13.8 g (113 mmol) of DMAP, 41.5 mL (3.0 M in ether, 124 mmol) of isopropylmagnesium chloride, 8.50 g (53.2 mmol) of (1*S*, 5*S*)-(-)-verbenone **53** and 12.3 mL (113 mmol) of TMSCl afforded 12.0 g (52.6 mmol, 93%) of **62** as a yellow oil: (SiO_2, R_f 0.55, EtOAc: hexanes, 1:9); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.18 (m, 5 H), 3.21 (d, 1 H, *J* = 19.7 Hz), 2.85 (d, 1 H, *J* = 19.7 Hz), 2.72-2.66 (m, 1 H), 2.66-2.58 (m, 2 H), 1.50 (s, 3 H), 1.48 (s, 3 H), 1.43 (d, 1 H, *J* = 8.7 Hz), 1.18 (s, 3 H); MS (EI) *m/z* (rel intensity) 228 (M^+, 15), 213 (25), 131 (100), 91 (40); HRMS (EI) calcd for $C_{16}H_{20}O$ 228.1514, found 228.1508.



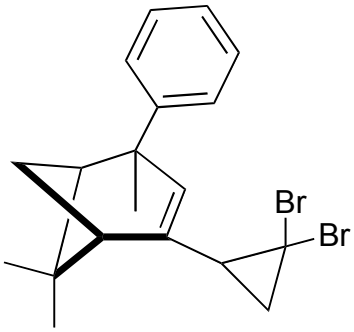
64

(1*R*,4*R*)-4,6,6-Trimethyl-2-phenyl-2-vinylbicyclo[3.1.1]heptan-2-ol (64).[39a] According to General Protocol A, 52.5 mL (1.0 M, 52.5 mmol) of vinylmagnesium bromide and 6.00 g (27.3 mmol) of **62** afforded **64** as a yellow oil. The crude product was used directly for the next step.



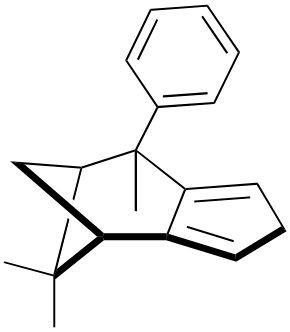
66

(1*R*,4*S*)-4,6,6-Trimethyl-4-phenyl-2-vinylbicyclo[3.1.1]hept-2-ene (66).[41a] According to General Procedure A, 6.12 g (23.9 mmol) of **64**, and 50.0 g of basic alumina gave 5.26 g (22.0 mmol, 46%) of **66** as a colorless oil: (SiO_2, R_f 0.8, EtOAc:hexanes, 1:9); ^{1}H NMR (500 MHz, C_6D_6) δ 7.24-7.17 (m, 4 H), 7.08-7.03 (m, 1 H), 6.50 (dd, 1 H, *J* = 17.4, 10.7 Hz), 5.70 (s, 1 H), 5.13 (d, 1 H, *J* = 17.4 Hz), 4.98 (d, 1 H, *J* = 10.7 Hz), 2.59 (app t, 1 H, *J* = 5.5 Hz), 2.28-2.21 (m, 1 H), 2.03 (dt, 1 H, *J* = 11.5, 5.7 Hz), 1.35 (s, 3 H), 1. 28 (s, 3 H), 1.22 (d, 1 H, *J* = 9.4 Hz), 1.05 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 151.2, 145.4, 138.3, 130.9, 126.7, 125.8, 111.4, 109.9, 53.4, 46.8, 42.0, 40.8, 30.5, 27.8, 26.6, 24.2.



68

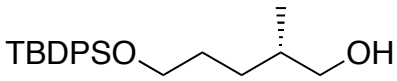
(1*R*,4*S*)-2-(2,2-Dibromocyclopropyl)-4,6,6-trimethyl-4-phenylbicyclo[3.1.1] hept-2-ene (68).[41a] According to General Protocol A, 3.46 g (14.5 mmol) of diene **66**, 7.34 g (29.1 mmol) of bromoform, 71.0 mg (0.312 mmol) of TEBA, 2 drops of ethanol and 7.60 mL (145 mmol) of a 50% NaOH solution yielded 3.40 g (8.30 mmol) of a colorless oil which was used in the next step without further purification.



70

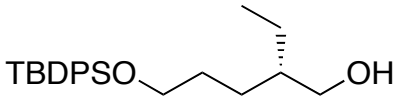
(1*S*,7*S*,8*S*)-7-Phenyl-7,9,9-trimethyltricyclo-[6.1.1]deca-2,5-diene (70).[41a] According to General Protocol A, 3.00 g (7.32 mmol) of dibromide **68**, and 21.0 mL (1.4 M in ether, 29.3 mmol) of methyllithium afforded 1.17 g (4.68 mmol, 64%) of crude **70** as a colorless oil: (Al_2O_3, R_f 0.6, pentane); $[\alpha]_D$ + 79.6 (*c* 1.9, hexanes, 24 °C) ^{1}H NMR (300 MHz, C_6D_6) δ 7.40-7.34 (m, 2 H), 7.23-7.12 (m, 2 H), 7.09 (m, 1 H), 6.12 (q, 1 H, *J* = 1.0 Hz), 5.86 (dd, 1 H, *J* = 1.6 Hz), 3.08 (d, 1 H, *J* = 23.8 Hz), 2.94 (d, 1 H, *J* = 23.8 Hz), 2.61 (t, 1 H, *J* = 5.1 Hz), 2.25-2.10 (m, 3 H), 1.63 (s, 3 H), 1.26 (s, 3 H), 0.93 (s, 3 H);

^{13}C NMR (75 MHz, C_6D_6) δ 152.2, 150.1, 149.5, 127.7, 127.1, 126.3, 125.8, 120.4, 53.9, 46.7, 43.8, 42.4, 41.0, 30.9, 27.8, 24.6; MS (EI) *m/z* (rel intensity) 251 ([M+1]$^+$, 10), 250 (M^+, 40), 181 (100), 129 (67), 105 (85), 91 (90); HRMS (EI) calcd for $C_{19}H_{22}$ 250.1721, found 250.1733.



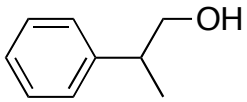
75

General Protocol B. (2*S*)-5-*Tert*-butyldiphenylsilanyloxy)-2-methyl-pentan-1-ol (75).[14b] A solution containing 9.00 mg (0.0154 mmol) of **71** and 127 μL (1.32 mmol) of $AlMe_3$ in 3.00 mL of CH_2Cl_2 was cooled to 0 °C and treated with 0.352 mL (0.462 mmol) of a 10% (by weight) solution of MAO in toluene. The reaction mixture was warmed to rt, then cooled to 0 °C and treated with a solution of 100 mg (0.31 mmol) of 1-(*tert*-butyldiphenylsilanyloxy)-4-pentene **74** in 2.00 mL of CH_2Cl_2. The reaction mixture was kept at 0 °C for 18 h before O_2 was vigorously bubbled through the solution. After all of the volatiles were removed, the remaining slurry was washed with a solution of 2 N NaOH and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated, and chromatographed on SiO_2 (R_f 0.6, EtOAc:hexanes, 1:4) to yield 60.0 mg (0.201 mmol, 65%) of **75** as a clear oil in 39% ee (OD Chiralcel, 0.5% ^{i}PrOH in hexanes as eluent (t_r = 43.4 and 51.6 min at a flow rate of 0.5 mL/min): $[\alpha]_D$ -3.6 (*c* 0.5, $CHCl_3$, 24 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.73-7.67 (m, 4 H), 7.49-7.35 (m, 6 H), 3.67 (t, 2 H, *J* = 6.4 Hz), 3.46 (ABX, dd, 2 H, *J* = 10.5, 6.4 Hz), 1.76-1.40 (m, 3 H), 1.31 (bs, 1 OH), 1.27-1.12 (m, 2 H), 1.06 (s, 9 H), 0.91 (d, 3 H, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 134.0, 129.5, 127.6, 68.2, 64.1, 35.4, 28.9, 29.2, 26.8, 19.2, 16.6; MS (EI) *m/z* (rel intensity) 299 ([M-C_4H_9]$^+$, 20), 281 (25), 269 (7), 229 (25), 221 (15), 200 (15), 199 (70), 139 (25) 135 (10), 105 (7), 83 (100), 77 (13); HRMS (EI) calcd for $C_{18}H_{23}O_2Si$ (M-C_4H_9) 299.1467, found 299.1475.



76

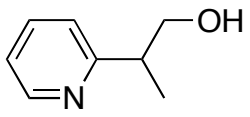
(2*S*)-5-*Tert*-butyldiphenylsilanyloxy)-2-methyl-pentan-1-ol (76). According to General Procedure B with the exception that 151 mg (1.32 mmol) of $AlEt_3$, 100 mg (0.31 mmol) of **74**, 9.00 mg (0.0154 mmol) of **71**, 352 μL (0.462 mmol) of MAO and 5.00 mL of CH_2Cl_2 afforded 49.0 mg (0.132 mmol, 43%) of **76** was obtained as a colorless oil in 34% ee (OD Chiralcel, 1% ^{i}PrOH in hexanes as eluent (t_r = 27.6 and 29.4 min at a flow rate of 0.5 mL/min): $[\alpha]_D$ -5.6 (*c* 0.5, $CHCl_3$, 24 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71-7.7 64 (m, 4 H), 7.56-7.32 (m, 6 H), 3.67 (t, 2 H, *J* = 6.3 Hz), 3.54 (bd, 2 H, *J* = 3.8 Hz), 1.67-1.52 (m, 3 H), 1.48-1.31 (m, 4 H), 1.24 (bs, 1 OH), 1.06 (s, 9 H), 0.90 (t, 3 H, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 134.0, 129.5, 127.6, 65.2, 64.2, 41.7, 29.7, 26.9, 26.4, 23.3, 19.2, 11.1; MS (EI) *m/z* (rel intensity) 313 $[M\text{-}C_4H_9]^+$ (10), 229 (10), 207 (7), 201 (5), 200 (5), 199 (65), 197 (15), 139 (30) 135 (15), 123 (6), 105 (10), 97 (100), 91 (15); HRMS (EI) calcd for $C_{23}H_{34}O_2Si$ $[M\text{-}C_4H_9]$ 313.1624, found 313.1651.



30

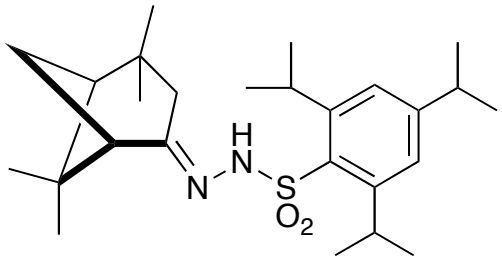
(*R*)-2-Phenylpropanol-1-ol (30).[17] According to General Protocol B, 28.0 mg (0.0480 mmol) of **71**, 297 mg (4.13 mmol) of $AlMe_3$, 1.00 mL (1.44 mmol) of MAO, 100 mg (0.960 mmol) of freshly distilled styrene **29** and 5.00 mL of CH_2Cl_2 afforded 70.0 mg (0.514 mmol, 54%) of **30** as a clear oil: $[\alpha]_D$ +10.6 (*c* 0.5, CH_2Cl_2, 24 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.31 (m, 2 H), 7.28-7.22 (m, 3 H), 3.72-3.58 (m, 2 H), 2.93 (app sext, 1 H, *J* = 6.9 Hz), 2.40 (bs, 1 OH), 1.30 (d, 3 H *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 128.9, 127.8, 126.9, 69.0, 42.7, 17.9; MS (EI) *m/z* (rel intensity) 136 (M^+, 35), 106 (40), 105 (100), 103 (25), 91 (26), 79 (30), 77 (35), 63 (6), 61 (23).

Esterification of 30 with α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA). Enantiomeric excess was determined by converting **30** to the Mosher ester: A solution of 5.00 mg (0.0370 mmol) of **30** and 17.7 μL (0.191 mmol) of Et_3N and 6.80 mg (0.0550 mmol) of DMAP in 1.00 mL of CH_2Cl_2 was added under N_2 to 41.1 mg (0.163 mmol) of (+)-MTPA-Cl. The reaction mixture was stirred for 12 h, diluted with CH_2Cl_2 and washed with 1 N HCl solution. The organic layers were dried ($MgSO_4$), filtered and concentrated to provide diastereomeric products with ^{1}H NMR (300 MHz, C_6D_6) signals at δ 1.08 (d, 3 H, *J* = 6.9 Hz), and 1.03 (d, 3 H, *J* = 7.0 Hz) in a ratio of 1.16:1.0, indicative of an ee of 7%.



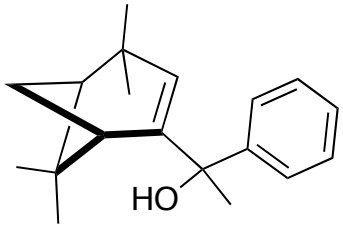
80

1-Pyridin-2-yl-propan-1-ol (80).[46] According to General Protocol B with the exception that the reaction was left for 24 h at 0 °C, 28.0 mg (0.0480 mmol) of **71**, 295 mg (4.01 mmol) of $AlMe_3$, 1.00 mL of a 10% (by weight) solution of MAO in toluene, 100 mg (0.951 mmol) of 2-vinylpyridine **79** and 5.00 mL of CH_2Cl_2 afforded 27.0 mg (0.197 mmol, 21%) of **80** as a yellow oil: $[\alpha]_D$ -0.12 (*c* 0.50, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, 1 H, *J* = 4.8 Hz) 7.70-7.63 (m, 1 H), 7.25 (d, 1 H, *J* = 8.5 Hz), 7.21-7.15 (m, 1 H), 4.69 (dd, 1 H, *J* = 7.0, 4.8 Hz), 4.28 (b, 1 OH), 1.93-1.81 (m, 1 H), 1.76-1.66 (m, 1 H), 0.94 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 148.1, 136.5, 122.2, 120.4, 73.8, 31.3, 9.4.



84

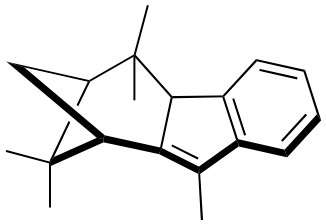
General Protocol C. (1*S*,5*S*)-(-)-4,4,6,6-Tetramethylbicyclo[3.1.1]hept-2-ylidene-2',4',6' triisopropyl benzenesulfonyl hydrazone (84).[50a,b] To a mixture containing 10.0 g (60.1 mmol) of **54** and 19.7 g (66.2 mmol) of 2,4,6-triisopropylbenzenesulfonyl hydrazide in 150 mL of acetonitrile was added 6.00 mL of conc. HCl (72.18 mmol) at rt. The reaction mixture was stirred at rt for 18 h, followed by evaporation of the volatiles in vacuo. The resulting oil was diluted with 200 mL $CHCl_3$ and washed with 150 mL of sat. aq. $NaHCO_3$ solution. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by chromatography on SiO_2 (R_f 0.6, EtOAc:hexanes, 1:9) to yield 15.8 g (49.3 mmol, 82%) of **84** as a white solid: Mp 156-159 °C (EtOAc:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (bs, 2 H), 4.20 (sept, 2 H, *J* = 6.8 Hz), 2.88 (sept, 1 H, *J* = 6.9 Hz), 2.53 (app t, 1 H, *J* = 5.4 Hz), 2.42-2.31 (m,1 H), 2.23 (d, 1 H, *J* = 19.0 Hz), 2.14 (d, 1 H, *J* = 6.9 Hz) 1.73-1.67 (m, 2 H), 1.40-1.30 (m, 23 H), 1.11 (s, 3 H), 1.01 (s, 3 H), 0.72 (s, 3 H); MS (EI) *m/z* (rel intensity) 446 (M^+, 75), 267 (100), 179 (75); HRMS (EI) calcd for $C_{26}H_{42}N_2O_2S$ 446.2967, found 446.3005.



85

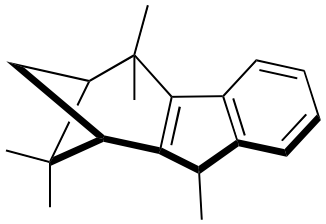
(1*S*,5*S*)-(-)-4,4,6,6-Tetramethyl-2-(1-hydroxy-1-methyl-1-phenyl)bicyclo [3.1.1]hept-2-ene (85).[50a,b] A solution containing 2.50 g (7.80 mmol) of **84** in 60.0 mL of

THF was treated with 10.7 mL (1.6 M in hexanes, 17.2 mmol) of ^{n}BuLi at -78 °C. The reaction mixture was stirred for 20 min at -78 °C, and at 0 °C for 15 min, then a solution of 0.910 mL (7.80 mmol) of acetophenone in 18.0 mL of THF was added dropwise. The reaction mixture was warmed to rt, and stirred for 4 h prior to quenching with 100 mL of water. The aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by chromatography on SiO_2 (R_f 0.4, Et_2O:hexanes, 1:4) to yield 1.33 g (4.92 mmol, 63%) of **85** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.37 (m, 2 H), 7.35-7.27 (m, 2 H), 7.25-7.18 (m, 1 H), 5.47 (app t, 1 H, *J* = 1.5 Hz), 2.21 (dt, 1 H, *J* = 11.3, 5.6 Hz), 2.06-2.00 (m, 1 H), 1.81-1.72 (m, 1 H), 1.62 (s, 3 H), 1.31 (dd, 3 H, *J* = 10.2, 5.4 Hz), 1.25 (s, 3 H), 1.12 (s, 3 H), 1.05 (s, 3 H), 0.94 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 146.2, 127.9, 126.5, 126.4, 125.4, 53.0, 43.9, 41.2, 38.2, 31.8, 30.5, 28.9, 27.4, 26.1, 25.1; MS (EI) *m/z* (rel intensity) 270 (M^+, 6), 252 (31), 212 (50), 135 (55), 121 (100), 107 (55), 105 (46), 91 (40); HRMS (EI) calcd for $C_{19}H_{26}O$ 270.1984, found 270.1993.



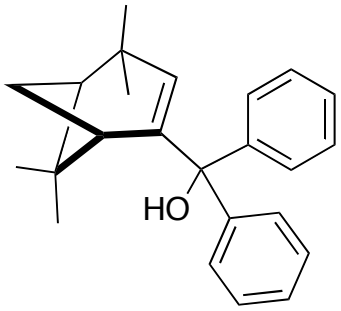
87

[1*S*-(1α,3α,4aβ)]-2,3,4,4a-Tetrahydro-2,2,4,4,9-pentamethyl-1,3-methano-*1H*-fluorene (87).[50a,b] To a solution of 1.21 g (4.47 mmol) of **85** in 70.0 mL of CH_2Cl_2 was added 3.45 mL (44.7 mmol) of TFA dropwise at 0 °C. After 30 min, 50 mL of sat. aq. $NaHCO_3$ solution and 100 mL of water were added. The aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried (Na_2SO_4), filtered and concentrated. The resulting crude yellow oil was used directly in the next step.



82

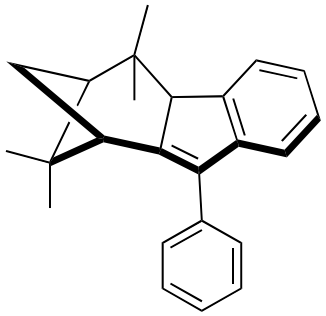
[1*S*-(1α,3α,4aβ)]-2,2,4,4,9-Pentamethyl-1,2,3,4-tetrahydro-1,3-methano-*1H*-fluorene (82).[50a,b] A solution containing 1.90 g (7.53 mmol) of **87** in 10.0 mL of pyridine was heated at reflux for 18 h. The reaction mixture was cooled to rt, diluted with EtOAc and treated with 1 N HCl solution. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with H_2O, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by chromatography on Al_2O_3 (R_f 0.90, pentane) to yield 1.31 g (5.19 mmol, 69%) of **82** as a clear oil: $[\alpha]_D$ +16.2 (*c* 1.0, hexanes, 24 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, 2 H, *J* = 7.8 Hz), 7.21 (t, 1 H, *J* = 7.3 Hz), 7.15 (t, 1 H, *J* = 7.5 Hz), 3.22 (q, 1 H, *J* = 7.5 Hz), 2.60-2.51 (m, 2 H), 1.95 (app t, 1 H, *J* = 5.8 Hz), 1.54 (d, 2 H, *J* = 6.6 Hz), 1.48 (s, 3 H), 1.47 (s, 3 H), 1.36 (s, 3 H), 1.31 (d, 3 H, *J* = 7.6 Hz), 0.95 (s, 3 H); MS (EI) *m/z* (rel intensity) 252 (M^+, 75), 209 (100), 181 (50); HRMS (EI) calcd for $C_{19}H_{24}$ 252.1878, found 252.1871.



86

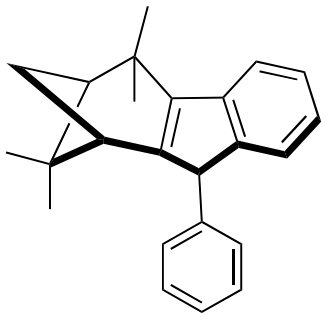
(1*S*,5*S*)-(-)-4,4,6,6-Tetramethyl-2-(1-hydroxy-1,1-diphenyl)bicyclo[3.1.1]hept-2-ene (86).[50a,b] According to General Protocol C, 6.00 g (18.7 mmol) of **84**, 3.37 g (18.7

mmol) of benzophenone and 20.6 mL (2.0 M in hexanes, 41.2 mmol) of ^{n}BuLi afforded **86** as a crude yellow oil which was used in the next step without further purification.



88

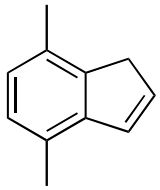
[1*S*-(1α,3α,4aβ)]-9-Phenyl-2,3,4,4a-tetrahydro-2,2,4,4–pentamethyl-1,3-methano-*1H*-fluorine (88).[50a,b] According to General Protocol C, 10.0 g (30.1 mmol) of **86** and, 23.0 mL (301 mmol) of TFA in 100 mL of CH_2Cl_2 afforded 8.08 g (25.6 mmol, 85%) of crude **88** as a clear oil (SiO_2, R_f 0.6, hexanes): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.12 (m, 9 H), 4.21 (s, 1 H) 3.22 (app t, 1 H, *J* = 5.2 Hz), 2.72-2.55 (m, 1 H), 1.90 (app t, 1 H, *J* = 5.2 Hz), 1.62 (s, 3 H), 1.46 (s, 3 H), 1.39 (s, 3 H), 1.23 (d, 1 H, *J* = 10.0 Hz), 0.87 (s, 3 H); MS (EI) *m/z* (rel intensity) 315 ([M+1]$^+$, 10), 314 (M$^+$, 40), 193 (100); HRMS (EI) calcd for $C_{24}H_{26}$ 314.2034, found 314.2031.



83

[1*S*-(1α,3α,4aβ)]-9-Phenyl-2,3,4,4-tetramethyl-1,2,3,4-tetrahydro-1,3-*1H*-fluorene (83).[50a,b] According to the General Protocol C, 5.08 g (16.1 mmol) of **88** and

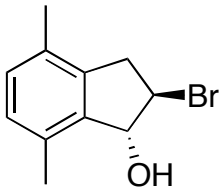
100 mL of pyridine afforded 1.50 g (4.77 mmol, 29%) of **83** as a colorless oil and as a 1.8:1 mixture of inseparable distereomers: (SiO_2, R_f 0.7, hexanes); $[\alpha]_D$ + 25.7 (*c* 1.0, hexanes, 24 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.36 (m, 2 H), 7.30- 7.12 (m, 9 H), 7.10- 6.98 (m, 5 H), 4.41 (s, 1.3 H), 4.27 (s, 0.7 H), 2.60-2.42 (m, 2 H), 2.28 (dt, 2 H, *J* = 16.1, 5.3 Hz), 1.91 (app t, 1 H, *J* = 5.7 Hz), 1.87 (app t, 1 H, *J* = 5.7 HZ), 1.53 (dd, 3 H, *J* = 11.2, 9.1 Hz), 1.48 (s, 3H), 1.37 (s, 3 H), 1.32 (s, 3 H), 1.24 (s, 3 H), 0.97 (s, 3 H), 0.69 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 149.2, 128.9, 143.9, 143.2, 138.8, 138.5, 128.8, 128.6, 128.3, 128.2, 126.6, 126.5, 124.3, 123.9, 123.5, 119.5, 119.4, 57.1, 56.4, 55.9, 43.5, 42.8, 42.4, 42.2, 38.3, 32.4, 32.0, 28.7, 28.4, 27.6, 25.4, 25.0, 24.4, 24.3; MS (EI) *m/z* (rel intensity) 315 ([M+1]$^+$, 15), 314 (M$^+$, 60); 271 (15), 215 (20), 193 (100) 167 (25), 115 (20), 91 (20); HRMS (EI) calcd for $C_{24}H_{26}$ 314.2034, found 314.2026.



93

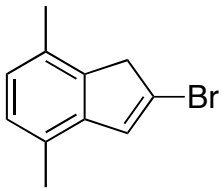
4,7-Dimethylindene (93).[54d] To 125 mL of MeOH was added 13.9 g (606 mmol) of sodium metal over 10 h at 0 °C, followed by 20.0 g (303 mmol) of cyclopentadiene **92**. The resulting red mixture was stirred for 1 h at rt then cooled to 0 °C, followed by addition of 24.2 g (212 mmol) of 2,5-hexanedione over 1 h at 0 °C. Stirring was continued for 10 h at rt. The reaction mixture was carefully quenched with 100 mL of water and neutralized with 1 N HCl. The aqueous phase was extracted with 100 mL of Et_2O (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting crude brown oil obtained was distilled at 65 °C (0.1 mmHg) to give 26.9 g (186 mmol, 62%) of **93** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16-1.12 (m 2 H), 7.06 (d, 1 H, *J* = 5.6 Hz), 6.69 (dt, 1 H, *J* = 5.6, 1.9 Hz), 3.41 (app t, 2 H, *J* = 1.9 Hz), 2.57 (s, 3 H), 2.47 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 142.1, 133.1, 130.4,

130.0, 127.6, 125.7, 38.1, 18.3, 18.2; MS (EI) *m/z* (rel intensity) 144 (M^+, 60), 129 (60); HRMS (EI) calcd for $C_{11}H_{12}$ 144.0939, found 144.0892.



94

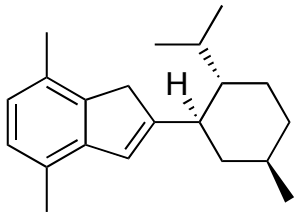
2-Bromoindan-4,7-dimethylindan-1-ol (94).[54d] To a solution of 1.00 g (6.93 mmol) of **93** and 249 μL of water in 5.20 mL of DMSO was added 1.23 g (7.07 mmol) of *N*-bromosuccinimide. The resulting orange mixture was allowed to warm to rt, and stirred for 45 min, and quenched with water at 0 °C. The aqueous phase was extracted with Et_2O (3x). The combined organic layers were washed with H_2O (5x), dried ($MgSO_4$), filtered and concentrated to yield 1.50 g (6.25 mmol, 90%) of **94** as a beige solid: Mp 93.1-95.6 °C (Et_2O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, 1 H, *J* = 7.6 Hz), 7.00 (d, 1 H, *J* = 7.6 Hz), 5.43 (dd, 1 H, *J* = 5.8, 2.6 Hz), 4.45 (app pent, 1 H, *J* = 3.5 Hz), 3.67 (dd, 1 H, *J* = 17.3, 6.5 Hz), 3.16 (dd, 1 H, *J* = 17.3, 3.5 Hz), 2.40 (s, 3 H), 2.23 (s, 3 H), 2.02 (d, 1 OH, *J* = 6.2 Hz); MS (EI) *m/z* (rel intensity) 240 (M^+, 30), 161 (100), 143 (100), 128 (45); HRMS (EI) calcd for $C_{11}H_{13}BrO$, 240.0150, found 240.0085.



95

2-Bromoindene (95).[54d] To a suspension of 26.3 g (110 mmol) of **94** in 98.0 mL of toluene was added 1.13 g (5.92 mmol) of TsOH. The reaction mixture was heated at reflux for 30 h, and water was removed by a Dean-Stark trap. The brown suspension

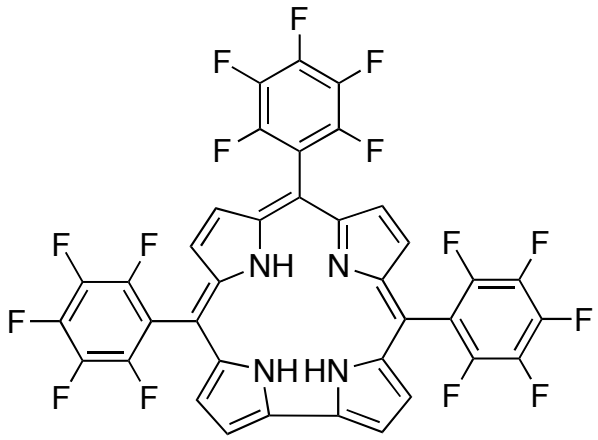
was filtered and the volatiles were removed under vacuum. The crude product was passed through a silica gel pad and washed with hexanes to give after concentration 17.5 g (78.4 mmol, 76%) of **95** as a white solid: Mp 88.1- 92.2 °C (hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (app t, 1 H, *J* = 1.4 Hz), 7.01 (d, 1 H, *J* = 7.7 Hz), 6.92 (d, 1 H, *J* = 7.7 Hz), 3.51 (bs, 2 H), 2.37 (s, 3 H), 2.30 (s, 3 H); MS (EI) *m/z* (rel intensity) 223 ($[M+1]^+$, 10), 222 (M^+, 30), 143 (100), 128 (45), 115 (35); HRMS (EI) calcd for $C_{11}H_{11}Br$ 222.0044, found 222.0045.



96

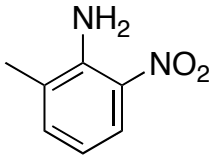
(-)-2-Menthyl-4,7-dimethylindene (96).[54d] To a suspension of 4.30 g (31.3 mmol) of $ZnCl_2$ in 30.0 mL of THF was added 38.0 mL (0.6 M in THF, 19.8 mmol) of (+)-menthylmagnesium chloride at 0 °C. After 1 h, 1.04 g (0.903 mmol) of tetrakis(triphenylphosphine)palladium(0) and 4.00 g (17.7 mmol) of **95** in 10.0 mL of THF were added in one portion. The resulting yellow mixture was warmed to rt and stirred for 48 h, before it was carefully quenched with 100 mL of sat. aq. NH_4Cl solution. The aqueous layer was extracted with 100 mL of Et_2O (4x). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by chromatography on SiO_2 (R_f 0.90, hexanes) and further purified by Kugelrohr distillation at 75 °C (1.5 mmHg) to yield 3.50 g (12.4 mmol, 70%) of **96** as a white solid: Mp 90.7-92.8 °C (hexanes); $[\alpha]_D$ – 47.7 (*c* 22.5, Et_2O, 24 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, 1 H, *J* = 7.6 Hz), 6.90 (d, 1 H, *J* = 7.6 Hz), 6.66 (bs, 1 H), 3.21 (AB, q, 2 H, *J* = 22.5 Hz), 2.56 (app dt, 1 H, *J* = 11.4, 3.3 Hz), 2.43 (s, 3 H), 2.36 (s, 3 H), 1.88-1.61 (m, 4 H), 1.60-1.44 (m, 1 H), 1.44-1.30 (m, 1 H), 1.27-1.11 (m, 2 H), 1.11-1.00 (m, 2 H), 0.96 (d, 3 H, *J* = 6.5 Hz), 0.84 (d, 3 H, *J* = 6.9 Hz), 0.79 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 153.7, 143.7, 141.3, 129.9, 127.6, 126.6, 124.9, 47.2, 43.9, 36.8, 35.3, 33.0, 27.8, 24.4, 22.6, 21.6, 18.4, 18.2, 15.3; MS (EI) *m/z* (rel intensity) 283 ($[M+1]^+$, 40), 282 (M^+, 100), 197 (75), 144 (80); HRMS (EI) calcd for $C_{21}H_{30}$ 282.2347, found 282.2352.



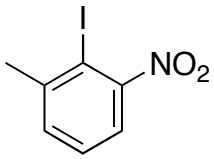
100

5,10,15-Tri(2,3,4,5,6-pentaflurophenyl) corrole (100).[65] To a solution of 4.00 g (20.4 mmol) of pentafluorobenzaldehyde **97** in 8.00 mL of CH_2Cl_2 was added 3.00 g of basic Al_2O_3 (oven activated) and 1.37 g (20.4 mmol) of pyrrole. The reaction mixture was allowed to stir at 60 °C open to air. After 4 h, the red paste was redissolved in 30.0 mL of CH_2Cl_2, and 2.32 g (10.2 mmol) of DDQ was added at rt. After 1 h, the reaction mixture was filtered through a pad of basic Al_2O_3 and the volatiles were concentrated. The crude product was purified by chromatography on Al_2O_3 (R_f 0.7, CH_2Cl_2:hexanes, 1:9) followed by recrystallization from 8.00 mL of CH_2Cl_2 to yield 583 mg (0.732 mmol, 11%) of **100** as a purple solid: UV/Vis (CH_2Cl_2) λ_{max} (ε x 10^{-3}) 413 (119), 565 (27.1), 608 nm (9.3); ^{1}H NMR (300 MHz, Acetone d_6) δ 9.20 (d, 2 H, J = 4.3 Hz), 9.12 (d, 2 H, J = 4.6 Hz), 8.91 (d, 2 H, J = 4.6 Hz), 8.74 (d, 2 H, J = 4.3 Hz); MS (EI) *m/z* (rel intensity) 796 (M^+, 100), 398 (10); HRMS (EI) calcd for $C_{37}H_{11}F_{15}N_4$ 796.0744, found 796.0759.



104

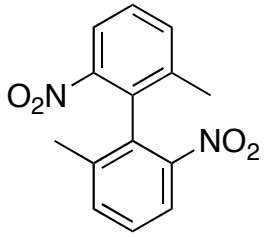
2-Amino-3-nitrotoluene (104).[73] To 112 mL of acetic acid was added 20.0 g (187 mmol) of *o*-toluidine **103** dropwise at 50 °C. After 30 min, the solution was cooled to 10 °C and 21.0 mL of conc. HNO_3 was added over 2 h. The reaction mixture was poured into a water-ice mixture and extracted with EtOAc. The organic layers were combined and concentrated. The brown solid was treated with 100 mL of conc. HCl and the reaction mixture was heated at reflux for 2 h prior to quenching with water. The precipitated product was filtered and dried under vacuum to yield 15.4 g (101 mmol, 54%) of **104** as a red solid: Mp 94 - 96 °C (H_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, 1 H, *J* = 7.7 Hz), 7.28 (d, 1 H, *J* = 7.2 Hz), 6.63 (dd, 1 H, *J* = 8.6, 7.1 Hz), 6.17 (bs, 2 NH), 2.24 (s, 3 H).



105

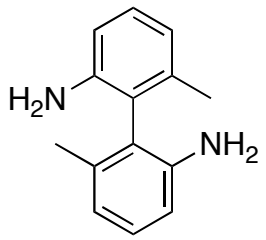
2-Iodo-3-nitrotoluene (105).[73] To 11.0 mL of conc. H_2SO_4 was added portion wise 5.00 g (32.9 mmol) of **104**. To this mixture was added 150 mL of sat. aq. $NaNO_2$ solution at 0 °C followed by 100 mL of a sat. aq. KI solution at 5 °C. The reaction mixture was allowed to stand for 18 h. The precipitates were filtered, dissolved in 100 mL of benzene, and washed with 200 mL water and a small amount of sat. aq. Na_2SO_3 solution. The combined organic layers were dried ($MgSO_4$), filtered and concentrated to give 7.94 (30.2 mmol, 92%) of **105** as a yellow solid: Mp 67.0 - 68.8 °C (benzene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.23 (m, 3 H), 2.55 (s, 3 H); MS (EI) *m/z* (rel intensity)

263 (M^+, 100), 217 (20), 90 (80); HRMS (EI) calcd for $C_7H_6INO_2$ 262.9443, found 262.9419.



106

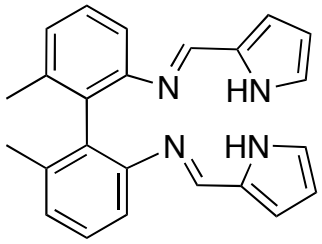
2,2'-Dimethyl-6,6'-dinitrobiphenyl (106).[73] To a solution of 5.00 g (19.0 mmol) of **105** in 50.0 mL of DMF was added 2.42 g (38.0 mmol) of copper powder in portions at 140 °C. The reaction mixture was stirred for 1.5 h, prior to quenching with water. The aqueous phase was extracted with Et_2O (5x), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to yield 3.80 g (13.9 mmol, 73%) of **106** as a yellow solid: Mp 107.1-108.9 °C (Et_2O); ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, 2 H, J = 7.8 Hz), 7.58 (d, 2 H, J = 7.0 Hz), 7.48 (d, 2 H, J = 8.0 Hz), 1.99 (s, 6 H); MS (EI) *m/z* (rel intensity) 272 (M^+, 20), 226 (100), 152 (30).



107

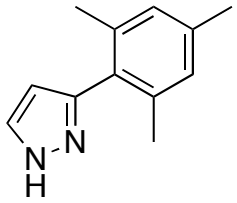
2,2'-Diamino-6,6'dimethylbiphenyl (AMB) (107).[73] To a solution of 1.80 g (6.61 mmol) of **106** in 150 mL of MeOH was added 0.100 g of 10% of palladium on activated carbon in one portion. The solution was degassed, flushed with argon, and stirred under hydrogen gas for 1 h at rt. The reaction mixture was filtered through a pad of Celite and volatiles were evaporated. The crude product was purified by chromatography on SiO_2

(R_f 0.6, EtOAc:hexanes, 1:4) to yield 1.20 g (5.65 mmol, 86%) of **107** as a white solid: Mp 135.0-137.6 °C (EtOAc:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (app t, 2 H, *J* = 7.7 Hz), 6.73 (d, 2 H, *J* = 6.9 Hz), 6.66 (d, 2 H, *J* = 7.9 Hz), 3.49 (m, 4 NH), 1.98 (s, 6 H); MS (EI) *m/z* (rel intensity) 212 (M^+, 100), 197 (60), 180 (35).



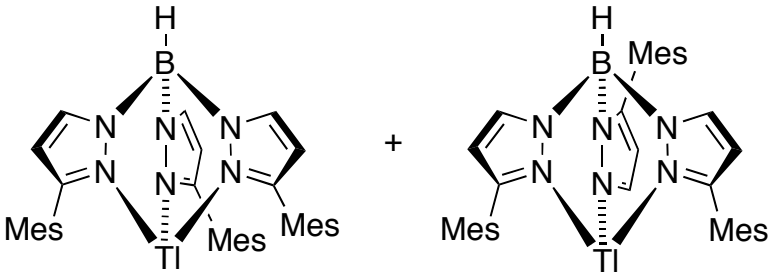
102

***N,N'*–(6,6'-Dimethylbiphenyl-2,2'diyl)bis(2-pyrrole-methyl)diimine (102).**[72] To a solution of 0.250 g (1.18 mmol) of **107** in 8.00 mL MeOH were added 0.224 g (2.36 mmol) of pyrrole-2-carboxaldehyde and 50.0 μL of HCOOH at rt. After 1 h, the reaction was concentrated and 10.0 mL of pentane was added. The mixture was stirred for 12 h. The product precipitated as a light red powder, which was filtered and washed with 10.0 mL of pentane to yield 0.413 g (1.12 mmol, 96%) of **102** as a 1.29:1 mixture of inseparable distereomers: Mp 118.7-122.6 °C (pentane); ^{1}H NMR (300 MHz, C_6D_6) δ 8.07 (bs, 1 H), 7.98 (bs, 1 H), 7.30-7.04 (m, 7 H), 6.90 (d, 1 H, *J* = 7.1 Hz), 6.81 (t, 2 H, *J* = 6.5 Hz), 6.75 (d, 1 H, *J* = 7.4 Hz), 6.59-6.50 (m, 3 H), 6.50-6.45 (m, 1 H), 6.29 (bs, 2 H), 6.17 (app t, 2 H, *J* = 2.7 Hz), 3.30 (bs, 4 NH), 2.15 (s, 3 H), 2.14 (s, 3 H), 2.09 (s, 3 H), 2.03 (s, 3 H); MS (EI) *m/z* (rel intensity) 367 ($[M+1]^+$, 50), 290 (100), 213 (60); HRMS (EI) calcd for $C_{24}H_{22}N_4$ $[M+1]^+$ 367.1923, found 367.1926.



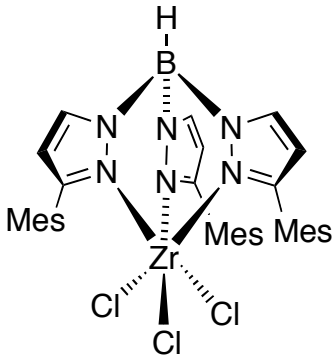
111

3-Mesityl-3*H*-pyrazole (111).[77] To a slurry containing 4.90 g (89.9 mmol) of anhydrous sodium methoxide in 112 mL of toluene was added a mixture of 14.5 g (89.4 mmol) of 2,4,6-trimethylacetophenone **110** and 4.00 mL of ethyl formate. After a few minutes, 20.0 mL of hexanes were added to the reaction mixture to facilitate stirring. After 1 h, the slurry was filtered and the white solid was washed with hexanes. The solid was dissolved in 120 mL of MeOH, and a solution of 9.40 g (89.9 mmol) of hydrazine hydrochloride in 40.0 mL of water was added over 10 min. Addition of 200 mL of cold water led to the precipitation of a yellow solid. The aqueous phase was extracted with 100 mL of CH_2Cl_2 (3x). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The resulting crude solid was treated with 2.25 g (44.9 mmol) of hydrazine hydrate and heated at reflux in 35.0 mL of isopropyl alcohol for 2 h. The volatiles were distilled off at 250 °C. The crude product was recrystallized from toluene to give 4.69 g (25.2 mmol, 28%) of **111** as a white solid: Mp 184.2 - 187.5 °C (toluene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, 1 H, J = 1.9 Hz), 6.89 (s, 2 H), 6.16 (d, 1 H, J = 1.9 Hz), 2.30 (s, 3 H), 2.02 (s, 6 H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 138.4, 138.0, 136.0, 129.3, 128.7, 128.5, 128.4, 128.3, 125.6, 106.0, 21.2, 20.4; MS (EI) *m/z* (rel intensity) 186 (M^+, 100), 158 (45), 144 (35); HRMS (EI) calcd for $C_{12}H_{14}N_2$ 186.1157, found 186.1122.



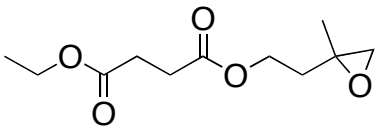
112a **112b**

Hydrotris(3-mesitylpyrazol-1-yl)borate thallium ($Tp^{Ms}Tl$) (112a, 112b).[77] A mixture of 4.71 g (25.3 mmol) of **111** and 683 mg (12.6 mmol) of KBH_4 in 10.0 mL of anisole was heated at reflux for 60 h. The excess anisole was distilled off at 250 °C, and the resulting solid was redissolved in 10.0 mL of THF. This solution was added to a stirred solution of 3.37 g (12.6 mmol) of $TlNO_3$ in 20.0 mL of water and 20.0 mL of CH_2Cl_2. After 1 h, the layers were allowed to separate. The aqueous layer was decanted and replaced with fresh water to remove emulsion. The aqueous phase was extracted with CH_2Cl_2 (3x). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated. The crude product was precipitated by addition of methanol. Evaporation of the mother liquor lead to a mixture of **112b** and unreactive **111**. The filtered crude product was recrystallized from toluene to give 7.4 g (9.60 mmol, 38%) of **112a** as a white solid: Mp 301.6- 304.9 °C (toluene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (bs, 3 H), 6.86 (s, 6 H), 6.09 (bs, 3 H), 2.29 (s, 9 H), 1.94 (s, 18 H), ^{13}C NMR (125 MHz, $CDCl_3$) 150.5, 137.3, 137.3, 135.8, 131.0, 127.9, 104.8, 21.1, 20.5; MS (EI) *m/z* (rel intensity) 772 ($[M+1]^+$, 30), 587 (100), 205 (80), 186 (50); HRMS (EI) calcd for $C_{36}H_{40}BN_6Tl$ 769.3167, found 769.3267.



109a

Hydrotris(3-mesitylpyrazol-1-yl)borate trichlorozirconium ($Tp^{Ms}ZrCl_3$) (109a).[75,76] A mixture of 611 mg (0.80 mmol) of **112a** and 300 mg (0.792 mmol) of $ZrCl_4(THF)_2$ in 50.0 mL of toluene was added at 24 °C. The resulting white suspension was stirred for 24 h at rt, and filtered through a fritted flask. The insoluble white powder was washed thoroughly with 20.0 mL of toluene. Evaporation of the mother liquor gave 93.0 mg (0.121 mmol, 15%) of **109b**. The filtered product was dried under vacuum for 24 h, to yield 442 mg (0.578 mmol, 72%) of **109a** as a white solid: Mp > 360°C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.98 (d, 3 H, *J* = 2.3 Hz), 7.25-7.15 (m, 4 H, Toluene), 6.84 (bs, 6 H), 6.14 (d, 3 H, *J* = 2.2 Hz), 2.34 (s, 3 H, Toluene), 2.29 (s, 9 H), 1.93 (s, 18 H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 149.4, 140.0, 139.3, 137.8, 128.8, 125.7, 108.4, 21.3, 20.6; MS (EI) *m/z* (rel intensity) 766 ($[M+1]^+$, 20), 765 (M^+, 16), 730 ($[M-Cl]^+$, 70), 579 ($[M-Tp^{Ms}]^+$, 25), 186 (45), 158 (28), 144 (21); HRMS (EI) calcd for $C_{36}H_{40}BClN_6Zr$ 761.1556, found 761.1629.

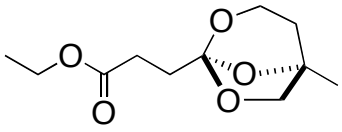


116

Ethyl ester 2-(2-methyloxiranyl)ethyl ester (116) [80] A solution of 300 mg (3.48 mmol) of 3-methyl-3-buten-1-ol in 6.00 mL of CH_2Cl_2 was cooled to 0 °C and treated

with 573 mg (3.48 mmol) of ethyl succinyl chloride. A solution of 704 mg (6.96 mmol) of Et_3N in 2.00 mL of CH_2Cl_2 was then added dropwise. The reaction mixture was stirred at 0 °C for 15 min. Et_2O was added and the mixture was washed with aq. 1 M HCl solution, 5% aq. $NaHCO_3$ solution and H_2O. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The resulting colorless oil was used directly in the next step.

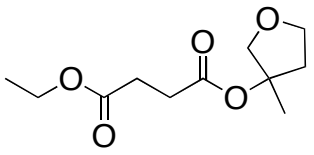
A solution of 275 mg (1.28 mmol) of succinic acid in 5.00 mL of CH_2Cl_2 was treated portionwise with 266 mg (1.54 mmol) of mCPBA at 0 °C. The mixture was stirred at 22 °C for 4 h and then cooled to 0 °C. The cooled mixture was filtered, and the filtrate was washed with aq. 1 N KOH solution and brine. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (R_f 0.6, EtOAc/hexanes, 1:4) to give 236 mg (1.27 mmol, 99%) of **116** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10-3.80 (m, 4 H), 2.37 (s, 4 H), 2.48-2.27 (m, 2 H), 1.76-1.60 (m, 2 H), 1.28 (s, 3 H), 1.18 (t, 3 H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 60.5, 59.9, 54.1, 52.8, 34.9, 28.4, 20.5, 13.6.



117

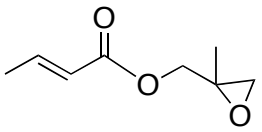
1-[2-(Ethoxycarbonyl)ethyl]-5-methyl-2,7,8-trioxobicyclo[3.2.1]octane (117).[80] A solution of 104 mg (0.452 mmol) of succinate **116** in 2.00 mL of CH_2Cl_2 was treated at 24 °C with 35.0 mg (45.0 μmol) of **109a**. The reaction mixture was stirred at 24 °C for 18 h, poured into sat. aq. $NaHCO_3$ solution, and extracted with CH_2Cl_2 (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The oily residue was purified by chromatography on SiO_2 (R_f 0.7, EtOAC/hexanes, 1:4) to give 64.0 mg (0.278 mmol, 62%) of **117** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (q, 2 H, J = 7.1 Hz), 4.07 (dd, 1 H, J = 9.1, 5.0 Hz), 4.01 (d, 1 H, J = 7.0 Hz), 3.84 (dd, 1 H, J = 11.4, 6.6 Hz), 3.49 (dd, 1 H, J = 7.1, 2.2 Hz), 2.53-2.43 (m, 2 H), 2.30-2.14

(m, 2 H), 2.11-1.96 (m, 1 H), 1.45 (dd, 1 H, J = 13.3, 4.1 Hz), 1.37 (s, 3 H), 1.25 (t, 3 H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 119.9, 78.6, 73.8, 60.1, 59.0, 33.7, 30.5, 28.7, 21.8, 14.1.



118

Ethyl 3-methyltetrahydrofuran-3-yl succinate (118).[79a, 80] A solution of 75.0 mg (0.325 mmol) of succinate **116** in 3.00 mL of CH_2Cl_2 was treated at 24 °C with 25.0 mg (0.0325 mmol) of **109a** and 0.600 mg (3.20 μmol) of $AgClO_4$. The reaction mixture was stirred at 20 °C for 18 h, poured into sat. aq. $NaHCO_3$ solution, and extracted with CH_2Cl_2 (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The oily residue was purified by chromatography on SiO_2 (R_f 0.3, EtOAc/hexanes, 1:4) to give 45.0 mg (0.195 mmol, 60%) of **118** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.13 (q, 2 H, J = 7.1 Hz), 3.99 (d, 1 H, J = 9.9 Hz), 3.90-3.80 (m, 2 H), 3.70 (d, 2 H, J = 9.9 Hz), 2.57 (s, 3 H), 2.36 (dt, 1 H, J = 12.9, 5.5 Hz), 1.97 (dt, 1 H, J = 13.4, 7.9 Hz), 1.60 (s, 3 H), 1.24 (t, 3 H, J = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 171.7, 86.9, 77.5, 67.1, 60.6, 39.3, 29.8, 29.1, 22.1, 14.1.

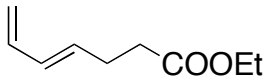


122

(*E*)-(2-Methyloxiran-2-yl)methyl but-2-enoate (122).[82] A solution of 692 mg (9.60 mmol) of 2-methyl-2-propen-1-ol in 18.0 mL of CH_2Cl_2 was cooled to 0 °C and treated with 1.00 g (9.60 mmol) of *trans*-crotonyl chloride. A solution of 1.94 g (19.2 mmol) of Et_3N in 6.00 mL of CH_2Cl_2 was then added dropwise. The reaction mixture was

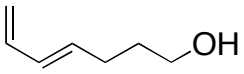
stirred at 0 °C for 30 min. Et_2O was added and the mixture was washed with aq. 1 N HCl solution, 5% aq. $NaHCO_3$ solution and H_2O. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The resulting colorless oil was used directly in the next step.

A solution of 940 mg (6.70 mmol) of succinic acid in 5.00 mL of CH_2Cl_2 was treated portionwise with 1.40 g (8.05 mmol) of mCPBA at 0 °C. The mixture was stirred at 22 °C for 4 h and then cooled to 0 °C. The cooled mixture was filtered, and the filtrate was washed with aq. 1 N KOH solution and brine. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (EtOAc/hexanes, 1:4) to give 988 mg (6.33 mmol, 94%) of **122** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90-5.73 (m, 1 H), 5.12-5.06 (m, 1 H), 5.04 (app t, 1 H, *J* = 1.3 Hz), 4.16 (d, 1 H, *J* = 11.9 Hz), 3.85 (d, 1 H, *J* = 11.9 Hz), 3.02 (dt, 1 H, *J* = 2.6, 1.3 Hz), 2.65 (d, 1 H, *J* = 4.7 Hz), 2.54 (d, 1 H, *J* = 4.7 Hz), 1.26 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 129.6, 117.9, 66.5, 53.9, 50.9, 38.0, 17.7. MS (EI) *m/z* (rel intensity) 170 (M^+, 10), 140 (55), 101 (70), 85 (85), 68 (100); HRMS (EI) calcd for $C_9H_{14}O_3$ 170.0943, found 170.0940.



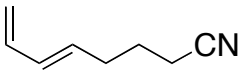
132

(*E*)-Ethyl hepta-4,6-dienoate (132).[84] A mixture of 1.50 g (17.8 mmol) of 1,4-pentadien-3-ol, 22.9 mL (125 mmol) of triethyl orthoacetate, and 266 μL (3.56 mmol) of propionic acid in 120 mL of toluene was heated at reflux for 18 h. Toluene was removed under vacuum to yield a yellow oil which was distilled *in vacuo* at 70 °C (0.2 mmHg) to afford 2.10 g (13.6 mmol, 77%) of ester **132** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21 (dt, 1 H, *J* = 16.8, 10.1 Hz), 6.01 (dd, 1 H, *J* = 15.0, 10.0 Hz), 5.68-5.52 (m, 1 H), 5.03 (d, 1 H, *J* = 16.8 Hz), 4.91 (d, 1 H, *J* = 16.8 Hz), 4.05 (q, 2 H, *J* = 7.1 Hz), 2.40-2.28 (m, 4 H), 1.18 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 136.6, 132.3, 131.6, 118.2, 115.7, 64.0, 60.0, 33.5, 27.6, 14.0.



133

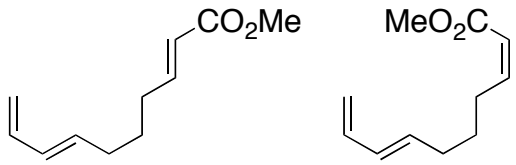
(*E*)-Hepta-4,6-dien-1-ol (133).[85] To a stirred suspension of 246 mg (6.50 mmol) of $LiAlH_4$ in 8.00 mL of Et_2O at 0 °C was added 1.00 g (6.50 mmol) of **132** in 6.00 mL of Et_2O. The reaction mixture was warmed to rt and after 1 h was quenched by sequential addition of MeOH and H_2O at 0 °C. The aqueous phase was extracted with Et_2O (3x). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated. The resulting colorless oil was used directly in the next step.



134

(*E*)-Octa-5,7-dienenitrile (134).[85] To a solution of 408 mg (3.60 mmol) of **133** and 546 mg (5.40 mmol) of Et_3N in 12.0 mL of CH_2Cl_2 was added 538 mg (4.70 mmol) of methanesulfonyl chloride at 0 °C. The reaction mixture was stirred at 0 °C for 2 h prior to being quenched with ice cold aq. 1 N HCl. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with sat. aq. $NaHCO_3$ solution, dried (Na_2SO_4), filtered and concentrated to give the crude mesylate. This crude material was combined with 433 mg (6.60 mmol) of KCN in 4.00 mL (80:20 EtOH-H_2O), and this mixture was heated at reflux for 18 h. The reaction mixture was quenched with brine. The aqueous layers were extracted with Et_2O (3x). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was purified by chromatography on SiO_2 (R_f 0.5, EtOAc:hexanes, 1:4) to yield 228 mg (1.88 mmol, 52%) of **134** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (dt, 1 H, *J* =16.8, 10.2 Hz), 6.09 (dd, 1 H, *J* = 15.0, 10.4 Hz), 5.66-5.50 (m, 1 H), 5.12 (d, 1 H, *J* = 16.8 Hz), 5.00 (d, 1 H, *J* = 10.8 Hz), 2.32 (t, 2 H, *J* = 7.1 Hz), 2.22 (AB q, 2 H, *J* = 7.1 Hz), 1.81-1.77 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.4, 132.7, 131.6, 119.3, 115.9, 30.9,

24.6, 16.2; MS (EI) *m/z* (rel intensity) 121 (M^+, 60), 81 (100), 80 (75), 79 (50), 66 (100). HRMS (EI) calcd for $C_8H_{11}N$ 121.0891, found 121.0895.

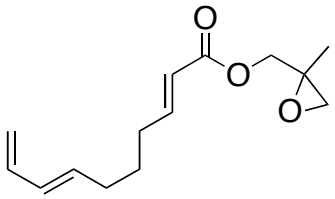


135a **135b**

(2*E*,7*Z*)-Methyl deca-2,7,9-trienoate (135a).[85] To a solution of 566 mg (4.67 mmol) of **134** in 9.30 mL of Et_2O was added 7.00 mL (7.00 mmol) of DIBAL (1.0 M in hexanes) at 0 °C. The reaction mixture was warmed to rt and stirred for 3 h. The solution was cooled to 0 °C and 10.0 mL of MeOH was added followed by 10.0 mL of aq. 1 M HCl solution. This two-phase mixture was stirred for 2 h at rt. The aqueous layer was extracted with Et_2O (3x). The combined organic layers were washed with sat. aq. $NaHCO_3$ solution, dried (Na_2SO_4), filtered and concentrated to give crude aldehyde. The crude aldehyde was treated with 1.70 g (5.14 mmol) of methyl (triphenyl phosphoranylidene) acetate in 8.00 mL of CH_2Cl_2 at rt. The reaction mixture was allowed to stir for 18 h at rt and then the solvent was removed *in vacuo*. The crude residue was purified by chromatography on SiO_2 (R_f 0.80, Et_2O:hexanes, 1:9) to yield 444 mg (2.46 mmol, 53%) of **135a** as a clear oil and 42 mg (0.24 mmol, 5%) of **135b** as a colorless oil. **135a:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (dt, 1 H, *J* = 8.6, 7.1 Hz), 6.29 (dt, 1 H, *J* = 16.9, 10.2 Hz), 6.04 (dd, 1 H, *J* = 15.1, 10.4 Hz), 5.81 (d, 1 H, *J* = 15.7 Hz), 5.75-5.55 (m, 1 H), 5.09 (d, 1 H, *J* = 16.9 Hz), 4.95 (d, 1 H, *J* = 10.1 Hz), 3.71 (s, 3 H), 2.20 (AB, q, 2 H, *J* = 7.5 Hz), 2.10 (AB, q, 2 H, *J* = 7.1 Hz), 1.65-1.48 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 149.1, 136.9, 134.0, 131.9, 121.1, 115.1, 51.3, 31.7, 31.5, 27.3.

(2*Z*,7*Z*)-Methyl deca-2,7,9-trienoate 135b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.40-6.14 (m, 2 H), 6.06 (dd, 1 H, *J* = 15.1, 10.7 Hz), 5.78 (dt, 1 H, *J* = 2.9, 1.4 Hz), 5.75-5.60 (m, 1 H), 5.09 (d, 1 H, *J* = 16.9 Hz), 4.96 (d, 1 H, *J* = 11.9 Hz), 3.71 (s, 3 H), 2.73-2.58

(m, 2 H), 2.13 (AB, q, 2 H, J = 7.2 Hz), 1.65-1.48 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 150.3, 137.1, 134.5, 131.4, 119.5, 114.9, 50.9, 32.1, 28.5.



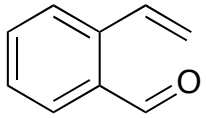
124

(2*E*,7*Z*)-(2-Methyloxiran-2-yl)methyl deca-2,7,9-trienoate (124).[86] To a solution of 375 mg (2.10 mmol) of **135a** in 15.0 mL of THF was added 10.0 mL of aqueous 1.5 N NaOH solution. The mixture was heated for 8 h at 70 °C, cooled to rt, diluted with sat. aq. $NaHCO_3$ solution, and washed with Et_2O (3x). The aqueous layer was cooled to 0 °C and acidified to pH 1 with aq. 6 N HCl solution. The reaction mixture was extracted with CH_2Cl_2 (3x), and the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 316 mg of a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.4 (bs, 1 H), 7.06 (dt, 1 H, J = 13.9, 6.9 Hz), 6.30 (dt, 1 H, J = 16.9, 10.2 Hz), 6.05 (dd, 1 H, J = 10.4 Hz), 5.83 (dt, 1 H, J = 2.8, 1.4 Hz), 5.75-5.55 (m, 1 H), 5.09 (d, 1 H, J = 16.7 Hz), 4.97 (d, 1 H, J = 10.0 Hz), 2.30-2.16 (m, 2 H), 2.11 (AB, q, 2 H, J = 7.1 Hz), 1.64-1.50 (m, 2 H).

To a solution of 316 mg of the above acid in 10.0 mL of toluene was added 335 μL (3.89 mmol) of oxalyl chloride at rt. The reaction mixture was stirred for 18 h at rt and then concentrated *in vacuo* to give 351 mg of acid chloride as a clear, yellow oil, which was used without purification.

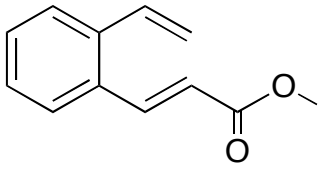
A solution of 167 mg (1.90 mmol) of (2-methyloxiran-2-yl) methanol in 4.00 mL of CH_2Cl_2 was cooled to 0 °C and treated with 351 mg (1.90 mmol) of acid chloride in 2.00 mL of CH_2Cl_2. A solution of 385 mg (3.84 mmol) of Et_3N in 2.00 mL of CH_2Cl_2 was then added dropwise. The reaction mixture was stirred at 0 °C for 15 min. Et_2O was added and the mixture was washed with aq.1 N HCl solution, 5% aq. $NaHCO_3$ solution and

H_2O. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was purified by chromatography on SiO_2 (R_f 0.6, EtOAc:hexanes, 1:9) to yield 354 mg (1.50 mmol, 79%) of **124** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (dt, 1 H, *J* = 16.7, 10.2 Hz), 6.10-5.90 (m, 1 H), 5.65-5.53 (m, 1 H), 5.53-5.43 (m, 1 H), 4.17 (d, 1 H, *J* = 11.9 Hz), 3.87 (dd, 1 H, *J* = 11.9, 2.0 Hz), 3.01 (dd, 2 H, *J* = 17.2, 5.0 Hz), 2.67 (d, 1 H, *J* = 4.7 Hz), 2.56 (d, 1 H, *J* = 4.7 Hz), 2.10-2.05 (m, 2 H), 1.29 (s, 3 H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 136.8, 133.8, 133.6, 132.2, 131.3, 131.1, 121.6, 120.8, 114.8, 114.7, 66.9, 54.3, 51.4, 37.4, 32.4, 31.8, 26.7, 18.0; MS (EI) *m/z* (rel intensity) 236 (M^+, 15), 169 (65), 120 (60), 106 (70), 79 (75), 66 (100). HRMS (EI) calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1417.



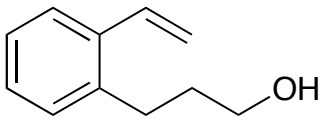
136

2-Vinylbenzaldehyde 136.[87] A solution of 3.41 mL (1.6 M in hexanes, 5.46 mmol) of ^{n}BuLi was added to a solution of 1.00 g (5.46 mmol) of 2-bromostyrene in 7.00 mL of THF at -78 °C. The reaction mixture was stirred for 1 h followed by the addition of a solution of 419 mg (5.73 mmol) of DMF in 2.00 mL of THF. The reaction mixture was stirred for 1 h at -78 °C and at rt for an additional 1 h prior to quenching with brine. The aqueous layer was extracted with $CHCl_3$ (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by chromatography on SiO_2 (R_f 0.50, EtOAc:hexanes, 1:9) to yield 515 mg (3.90 mmol, 71%) of **136** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.16 (s, 1 H), 7.69 (d, 1 H, *J* = 7.8 Hz),7.45-7.30 (m, 4 H), 5.62 (d, 1 H, *J* = 17.4 Hz), 5.38 (d, 1 H, *J* = 11.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 139.9, 133.3, 132.9, 132.4, 130.9, 127.5, 126.9, 118.8.



137

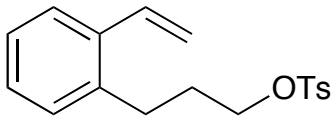
(*E*)-Methyl 3-(2-vinylphenyl)acrylate (137).[83] To a suspension of 167 mg (60% in mineral oil, 6.94 mmol) of sodium hydride in 10.0 mL of THF, 828 mg (4.54 mmol) of trimethyl phosphonoacetate was added dropwise at 0 °C. The resulting slurry was warmed to 24 °C and stirred for 30 min. The reaction mixture was cooled to -78 °C and 500 mg (3.79 mmol) of **136** in 2.00 mL of THF was added over 30 min. The mixture was then allowed to warm slowly to rt and stirred 14 h. The resulting white suspension was treated with sat. aq. NH_4Cl solution and washed with Et_2O (3x). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The crude product was purified by chromatography on SiO_2 (R_f 0.40, EtOAc:hexanes, 1:9) to yield 527 mg (2.80 mmol, 74%) of **137** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, 1 H, J = 15.9 Hz), 7.51 (dd, 2 H, J = 10.6, 7.7 Hz), 7.31 (ddd, 2 H, J = 21.5, 13.8, 6.6 Hz), 7.07 (dd, 1 H, J = 17.3, 11.0 Hz), 6.37 (d, 1 H, J = 15.7 Hz), 5.64 (d, 1 H, J = 17.3 Hz), 5.43 (d, 1 H, J = 11.0 Hz), 3.82 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 142.2, 137.7, 133.7, 133.8, 132.0, 129.7, 127.6, 126.7, 119.5, 117.8, 51.4.



138

3-(2-Vinylphenyl)propan-1-ol (138).[83] A solution of 527 mg (2.80 mmol) of **137** in 7.00 mL of THF was added to a suspension of 213 mg (5.60 mmol) of $LiAlH_4$ in 5.00 mL of THF at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. Excess $LiAlH_4$ was quenched with sat. aq. K, Na-tartrate tetrahydrate solution at 0 °C. The reaction mixture was stirred for an additional 1 h at rt. The suspension was then filtered through

a pad of Celite. The aqueous layer was extracted with Et_2O (3x), and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to yield 175 mg of a colorless oil which was used in the next step without further purification.



126

3-(2-Vinylphenyl)propyl 4-methylbenzenesulfonate(126).[83] To a solution of 175 mg (1.08 mmol) of **138** and 171 mg (2.16 mmol) of pyridine in 2.00 mL of CH_2Cl_2, 309 mg (1.62 mmol) of *p*-toluenesulfonyl chloride was added in one portion at 0 °C. The resulting mixture was stirred at 5 °C for 18 h. The resulting suspension was warmed to rt, diluted with H_2O and aq. 1 N HCl solution, and the aqueous layer was washed with Et_2O (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by chromatography on SiO_2 (R_f 0.40, EtOAc:hexanes, 1:4) to yield 211 mg (0.670 mmol, 62%) of **126** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, 2 H, *J* = 8.3 Hz), 7.47 (dd, 1 H, *J* = 7.2, 1.7 Hz), 7.35 (bd, 2 H), 7.25-7.10 (m, 2 H), 7.02 (dd, 1 H, *J* = 7.2, 1.5 Hz), 6.89 (dd, 1 H, *J* = 17.4, 10.9 Hz), 5.63 (dd, 1 H, *J* = 17.3, 1.4 Hz), 5.30 (dd, 1 H, *J* = 10.9, 1.4 Hz), 4.06 (t, 2 H, *J* = 6.1 Hz), 2.73 (t, 2 H, *J* = 7.4 Hz), 2.47 (s, 3 H), 1.98-1.84 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 137.7, 136.4, 134.1, 133.0, 129.8, 129.5, 127.8, 126.6, 125.9, 115.8, 69.7, 29.8, 28.8, 21.5.

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