HYDROZIRCONATION/ZR-ZN TRANSMETALATION/ALDIMINE ADDITION: ONE-POT SYNTHESIS OF ALLYLIC, *C*-CYCLOPROPYLALKYL, AND HOMOALLYLIC AMINES FROM ALKYNES.

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Abstract

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The Zr-Zn transmetalation, aldehyde addition methodology developed in the Wipf group was extended to the synthesis of allylic amines. The use of toluene as a reaction solvent was required to obtain high yields and low reaction times. *N*-Phosphinoyl-, *N*-sulfonoyl-, and *N*-carbamoylimines were excellent substrates for this transformation. Many chiral ligands were tested for asymmetric catalysis, but minimal *ee* was achieved. Addition to chiral phosphinimines was also attempted, but the diastereoselectivities were low.

A novel three-component *C*-cyclopropylalkylamine synthesis was discovered while attempting to perform the allylic amine synthesis in CH_2Cl_2. The mechanism of this transformation is not fully understood; however, this is the first reported example of a high-yielding Simmons-Smith cyclopropanation with CH_2Cl_2 as the carbene precursor. This reaction was optimized by adding CH_2I_2 to the reaction mixture once all imine was consumed. Addition of CH_2I_2 prior to imine substrate resulted in homoallylic amine formation.

List of Abbreviations

Ac .....acetyl

BDPS.....*tert*-butyldiphenylsilyl

Bn.....benzyl

Boc .....*tert*-butyloxycarbonyl

cat. .....catalytic

Cbz .....benzyloxycarbonyl

cod.....1,5-cyclooctadiene

Cp.....cyclopentadienyl

dba.....dibenzylideneacetone

DBU .....1,8-diazabicyclo[5.4.0]undec-7-ene

DEAD .....diethyl azodicarboxylate

DEIPS .....diethylisopropylsilyl

DEPC .....diethyl cyanophosphonate

DMAP 4-dimethylaminopyridine

DME.....ethylene glycol dimethyl ether

DMF .....*N*,*N*-dimethylformamide

DMP .....Dess-Martin periodinane

DMSO .....dimethylsulfoxide

DPPA .....diphenylphosphoryl azide

dppf .....1,1'-bis(diphenylphosphino)ferrocene

dr .....diastereomeric ratio

ee .....enantiomeric excess

ent.....enantiomer

HPLC .....high pressure liquid chromatography

KHMDS .....potassium bis(trimethylsilyl)amide

L* .....chiral ligand

NIS .....*N*-iodosuccinimide

NMO .....4-methylmorpholine *N*-oxide

PG .....protecting group

PMB 4-methoxybenzyl

p-Tol.....4-tolyl

rt .....room temperature

TBAF .....tetrabutylammonium fluoride

TBS .....*tert*-butyldimethylsilyl

TES .....triethylsilyl

Tf.....trifluoromethanesulfonyl

TFA .....trifluoroacetic acid

THF .....tetrahydrofuran

TIPS .....triisopropylsilyl

TLC .....thin layer chromatography

TMS .....trimethylsilyl

TPAP.....tetrapropylammonium perruthenate

Ts.....*p*-toluenesulfonyl

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1. Introduction

1.1. Hydrozirconation[1]

Hydrozirconation with Cp_2ZrHCl (Schwartz reagent) is one of the few general methods available for the direct conversion of readily available alkenes and alkynes into organometallic reagents (Figure 1).[2] Another advantage zirconocenes have over other organometallics are reaction conditions that are compatible with the presence of many functional groups. The majority of synthetic applications utilize alkenylzirconocenes (**4**), since the reaction of Cp_2ZrHCl with alkynes is very fast and highly regioselective, whereas alkenes are not as reactive, and furthermore internal alkylzirconocenes are rapidly isomerized into terminal alkylzirconocenes.[3] If this isomerization can be avoided, the hydrozirconation of an internal alkene generates a stereocenter, but very little effort has been made towards asymmetric hydrozirconation.[4]

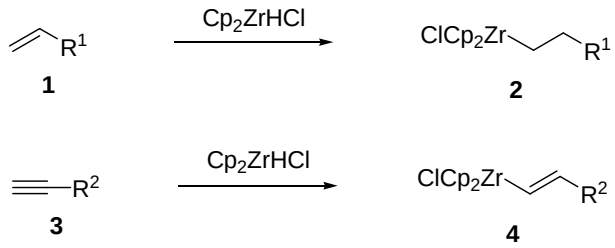


Figure 1. Hydrozirconation to form alkyl- and alkenylzirconium reagents.

While hydrozirconation is the most common method for forming organozirconocenes, Cp_2ZrEt_2 and Cp_2ZrBu_2 (easily prepared by reacting Cp_2ZrCl_2 with the appropriate alkyllithium reagent) can be used to form zirconacyclopentanes, -cyclopentenes, and -cyclopentadienes,[5] which then react very similarly to acyclic organozirconocenes. Cp_2ZrR_2 reagents can also be inserted into vinyl halides,[6] methoxy enol ethers,[7] enolsilanes,[8] and vinyl sulfides, sulfoxides, and sulfones[9] to form alkenylzirconocenes.

Cp_2ZrHCl was first prepared in 1970[10] and used to hydrozirconate alkenes[11] and alkynes[12] by Wailes and co-workers. Subsequently, Schwartz and co-workers treated the resulting alkyl-[13] and alkenylzirconocenes[14] with inorganic electrophiles, and used trans-metalation (from Zr to Al) to increase their reactivity towards organic electrophiles.[15] Schwartz reagent is a moderately air-, moisture-, and light-sensitive colorless solid that can be handled and

weighed on a balance. The hydrozirconation of terminal alkynes proceeds rapidly (5-15 min) at room temperature in CH_2Cl_2 or THF, and is very easily monitored visually since Cp_2ZrHCl is insoluble in most organic solvents whereas the colored organozirconocenes **4** are highly soluble.

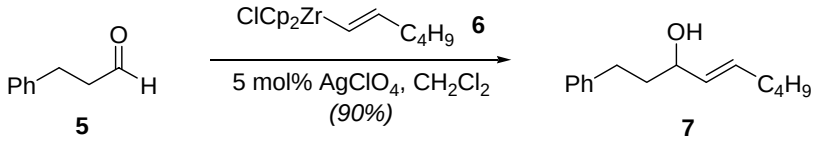
In general, amides, ketones, aldehydes and nitriles are not compatible with hydrozirconation conditions, but alkynes can be selectively hydrozirconated in the presence of certain esters. Functional groups that are recovered unchanged after exposure to Schwartz reagent include carbamates, acetals, epoxides, ethers, halides, and sulfides. Alcohols undergo an acid-base reaction with one equivalent of Cp_2ZrHCl and thereafter do not significantly interfere with alkene or alkyne hydrozirconation. Schwartz reagent has been used as a reducing agent by Ganem and co-workers for the deoxygenation of β-ketoesters to α,β-unsaturated esters,[16] and for the reduction of amides to imines.[17] Cp_2ZrHCl also reduces *N*,*N*-disubstituted amides to aldehydes,[18] and phosphine oxides to phosphines.[19]

Though the ionic character of the C-Zr bond is almost equivalent to that of the C-Mg bond, organozirconocenes are much weaker nucleophiles than Grignard reagents due to steric shielding at the metal center by the two cyclopentadienyl ligands. Small electrophiles such as halogens, protons, dioxygen, CO,[20] and isocyanides,[21] can be directly added to the C-Zr bond. One of the most widely used applications of organozirconocenes is for the preparation of (*E*)-vinyl halides by alkyne hydrozirconation followed by halogenation. (*Z*)-Vinyl halides can also be prepared by hydrozirconating stannylacetylenes.[22] Regiospecific deuterium labeling can be achieved by quenching organozirconocenes with D_2O or by using Cp_2ZrDCl for hydrozirconation.[23] Hanzawa, Taguchi and co-workers have developed the synthetic utility of acylzirconocenes (formed by CO insertion into the C-Zr bond) and demonstrated their reactivity in aldehyde additions,[24] imine additions,[25] Pd-catalyzed cross-coupling,[26] and Pd-catalyzed 1,2- or 1,4-additions to α,β-unsaturated ketones.[27]

Suzuki and co-workers have prepared allylzirconocenes by hydrozirconation of allenes. These reagents readily converted aldehydes into homoallylic alcohols in high diastereoselectivities.[28] Along with acylzirconocenes, however, allylzirconocenes are the only classes of organozirconium reagents that will react directly with organic electrophiles such as aldehydes.

One way to increase alkenylzirconocene reactivity towards organic electrophiles is to reduce the steric congestion about zirconium by chloride abstraction. Suzuki and co-workers reported that cationic zirconocenes prepared *in situ* reacted rapidly with aldehydes to generate

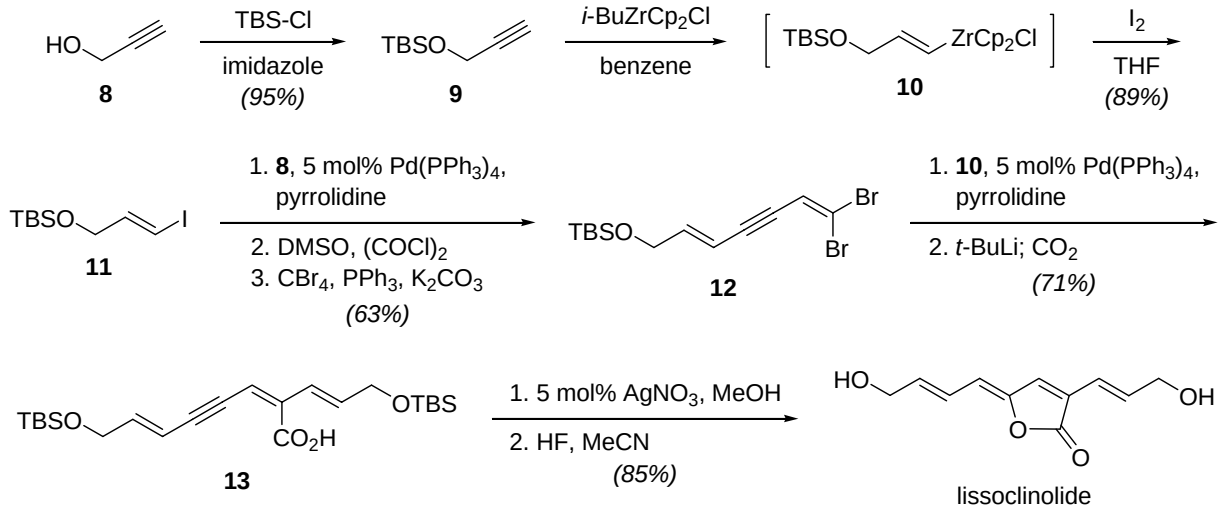
allylic alcohols (Scheme 1).[29] For example, when **6**, the product of hydrozirconation of 1-hexyne, was treated with aldehyde **5** in the presence of 5 mol% of $AgClO_4$, alcohol **7** was isolated in 90% yield after only a 10 min reaction time. In the absence of the Ag(I) salt, only 17% conversion was observed after 2 h. Wipf and Xu have shown that cationic alkenylzirconocenes promote an epoxide rearrangement/[1,2]-hydrogen shift of terminal epoxides, followed by vinylation of the resulting aldehyde, affording secondary allylic alcohols.[30]



Scheme 1. Alkenylzirconocene addition to aldehydes catalyzed by $AgClO_4$.

A second general solution to the lack of reactivity of alkenylzirconocenes is transmetalation. Many metals can be used for transmetalation from alkyl- and alkenylzirconocenes;[b] however, the most synthetically useful are Pd and Ni, Cu, and Zn. Negishi and co-workers discovered that alkenylzirconocenes could be coupled to aryl or alkenyl halides under Ni-[31] or Pd-catalysis.[32] A recent total synthesis of lissoclinolide demonstrates a typical application of this methodology (Scheme 2).[33] Protected propargyl alcohol **9** was hydrozirconated with an *in situ* generated reagent[34] and the resulting alkenylzirconocene **10** was iodinated to form (*E*)-vinyl iodide **11**. Pd-catalyzed coupling with propargyl alcohol **8**, Swern oxidation and then a Corey-Fuchs reaction converted **11** into 1,1-dibromide **12**. Pd-catalyzed Negishi coupling of vinyl bromide **12** with zirconocene **10** occurred exclusively at the *trans*-position. Carboxylic acid **13** was then formed by lithium-halogen exchange of the remaining vinyl bromide with a CO_2 quench. Finally, the natural product was formed by Ag^+-catalyzed lactonization of **13**, and deprotection. The Zr-Pd coupling methodology has aslo been used in a total synthesis of papulacandin.[35]

Fu and co-workers have extended the Pd-catalyzed coupling of alkenylzirconocenes to alkyl halides,[36] and Lipshutz and Frieman have recently reported that the heterogeneous Ni-catalyzed coupling of alkenylzirconocenes and aryl halides can be significantly accelerated by using microwaves.[37]



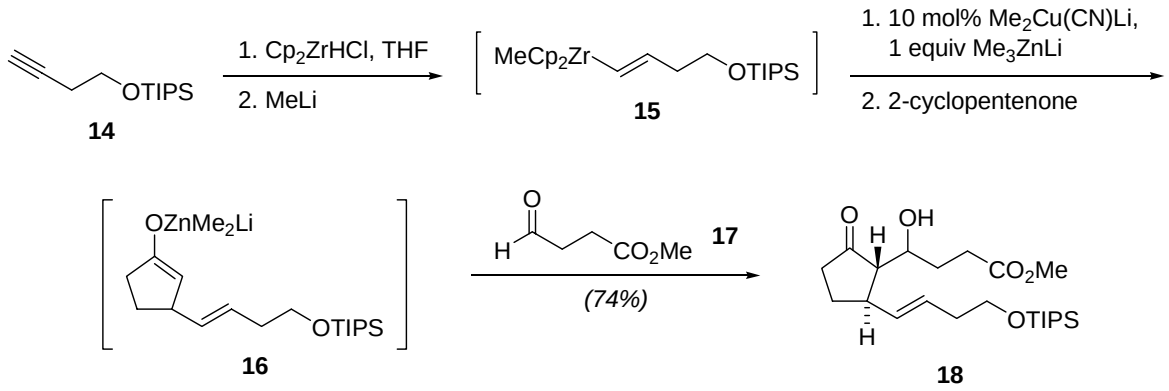
Scheme 2. Pd-catalyzed alkenylzirconocene and vinyl bromide coupling in Negishi's total synthesis of lissoclinolide.

Transmetalation from Zr to Cu combines the ease of preparation of organozirconocenes with the wide scope of reactions of organocopper reagents.[38] Wipf and co-workers showed that Cu(I)-catalyzed addition of alkenylzirconocenes to acid chlorides afforded α,β-unsaturated ketones,[39] and that Cu catalyzes the conjugate addition of alkylzirconocenes to enones.[40,41] Lipshutz and co-workers have worked extensively on the preparation of cyanocuprates using a hydrozirconation, transmetalation sequence.[42] These cuprate reagents can be alkylated with epoxides or activated (benzylic or allylic) halides,[43] and used in conjugate additions to α,β-unsaturated ketones.[44] Lipshutz and Wood reported a three-component coupling of cyanocuprates, cyclopentenones and aldehydes (or propargylic triflates) for the synthesis of prostaglandin-like compounds (Scheme 3).[45] For example, disubstituted cyclopentenone **18** was prepared in one pot and 74% yield as a 12:1 mixture of stereoisomers using alkyne **14**, 2-cyclopentene-1-one and aldehyde **17**. The same sequence has also been performed on a solid support.[46]

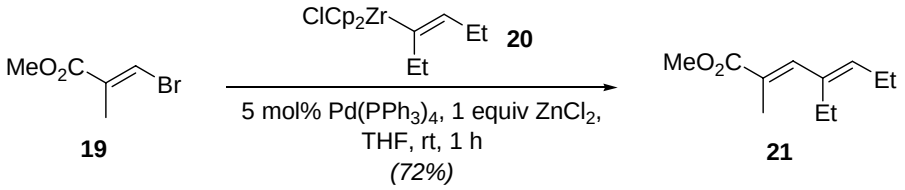
1.2. The Zr-Zn Transmetalation Methodology[47]

Negishi and co-workers discovered a significant acceleration in the Pd(0)-catalyzed cross coupling of alkenylzirconocenes with alkenyl, aryl, and alkynyl halides upon addition of $ZnCl_2$

to the reaction mixture (Scheme 4).[48] For example, the Pd(0)-catalyzed coupling of zirconocene **20** with vinyl bromide **19** yielded no trace of product after 6 h, whereas a 72% isolated yield of the desired diene **21** was obtained after 1 h when the reaction was performed in the presence of a stoichiometric amount of $ZnCl_2$. This acceleration is likely due to a transmetalation of the alkenyl organometallic from the large zirconocene to the much smaller zinc, followed by another transmetalation, to palladium, and continuing in the standard Pd(0)-coupling catalytic cycle.[49]



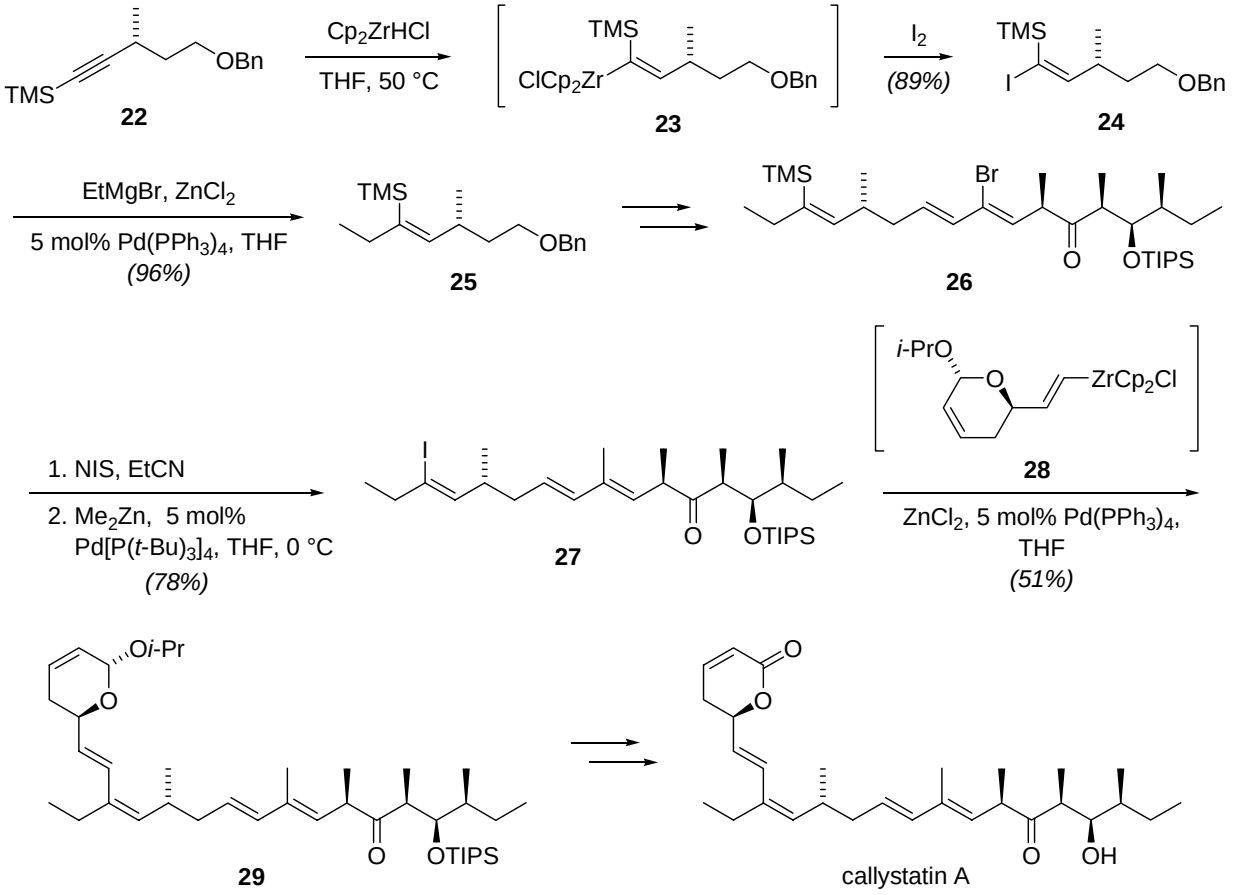
Scheme 3. One-pot synthesis of prostaglandins by conjugate addition, enolate trapping.



Scheme 4. $ZnCl_2$-accelerated coupling of alkenyl zirconocenes.

Panek and Hu optimized[50] this process for their synthesis of the unnatural amino acid Adda.[51] The recent total synthesis of callystatin A by Langille and Panek used a $ZnCl_2$-assisted sp^2-sp^2 coupling of an alkenylzirconocene, and a second hydrozirconation to prepare a (*Z*)-vinyl halide (Scheme 5).[52] Trimethylsilylalkyne **22** was hydrozirconated at 50 °C and the resulting terminal zirconocene **23** was quenched selectively at Zr with iodine, affording (*E*)-vinyl iodide **25**. Negishi coupling replaced the iodine with an ethyl group and, after several steps, iodo-desilylation and another Negishi coupling (selectively at the vinyl bromide) formed (*Z*)-vinyl iodide **27**. A second hydrozirconation was used to prepare alkenylzirconocene **28**, which was coupled to **27** to form the carbon skeleton of the natural product. Completion of the total

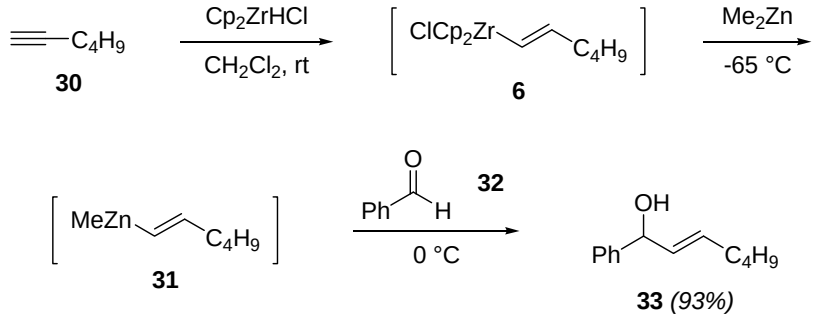
synthesis required only two deprotections and an oxidation. The Zr-Zn-Pd transmetalation sequence has also been used in the total syntheses of reveromycin B,[53] motuporin,[54] FR 901464,[55] eunicenone A,[56] β-carotene,[57] pitiamide A,[58] and xerulin.[59]



Scheme 5. Two applications of alkenylzirconocenes in Panek's total synthesis of callystatin A.

Wipf and Xu reported in 1993 a high yielding preparation of allylic alcohols from alkenylzirconocenes and aldehydes mediated by dialkylzinc reagents (Scheme 6).[60] For example, hexenyl zirconocene **6** was added to benzaldehyde in the presence of Me_2Zn to afford allylic alcohol **33** in 93% isolated yield (based on benzaldehyde). The reaction mechanism is thought to involve a Zr-Zn transmetalation, forming alkenyl zinc species **31**, followed by a Zr-accelerated[61] 1,2-addition of exclusively the alkenyl group of **31** to aldehyde **32**.[62] When the reaction solvent is CH_2Cl_2, this one-pot reaction is completed within 10 h on an 18 mmol scale.[63] Substituted benzaldehydes and aliphatic aldehydes were also effective electrophiles, and

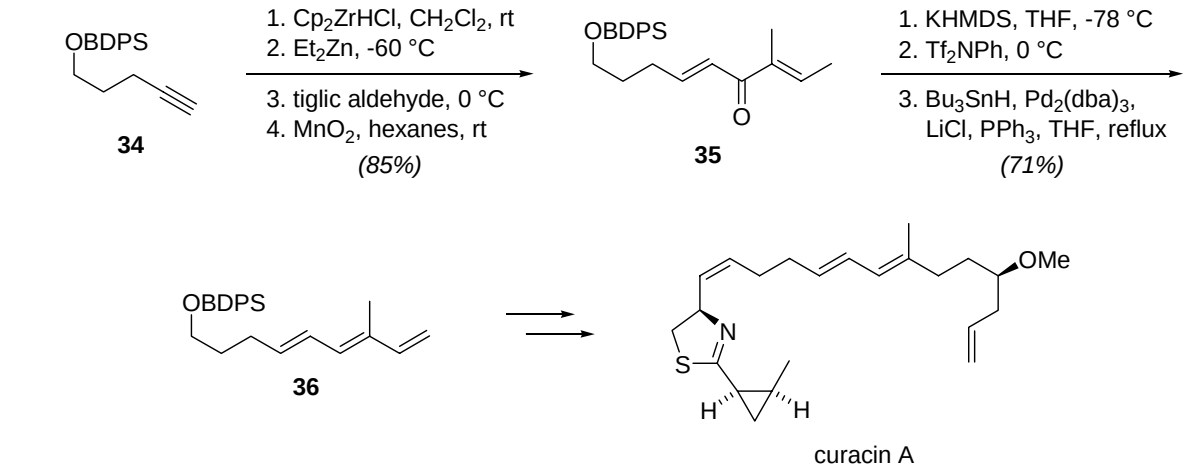
functional groups tolerated on the alkynes included silyl ethers and benzyl esters. The allylic alcohols were isolated in 54-94% yield. Me_2Zn can be used in catalytic quantities,[64] and this same net transformation has been shown to be mediated by both $ZnBr_2$[65] and MeLi.[66]



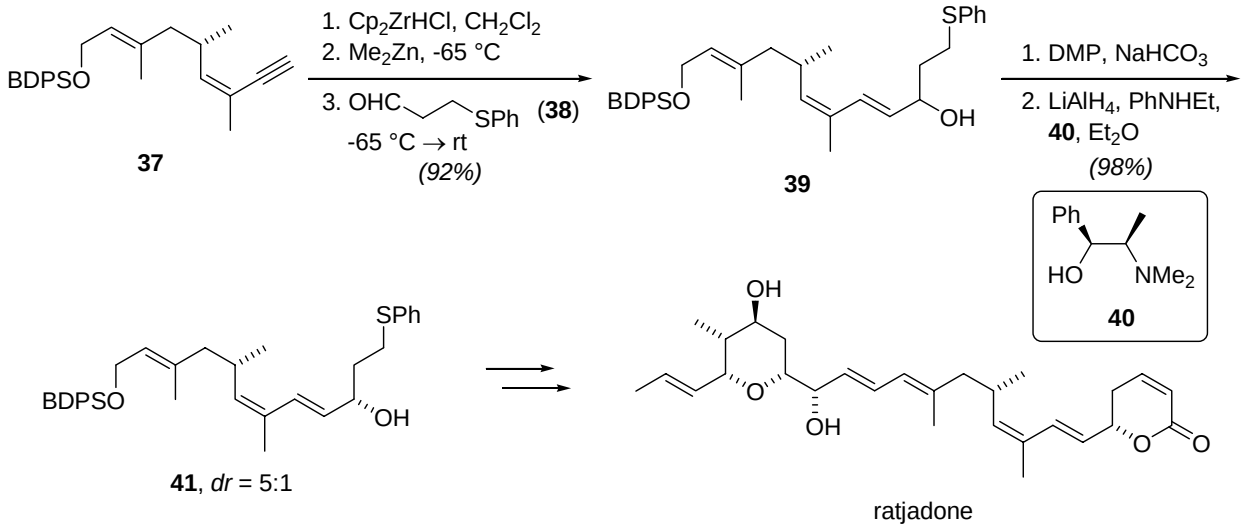
Scheme 6. Zr-Zn transmetalation and *in situ* addition to aldehydes.

Wipf and Xu used the Zr-Zn transmetalation/aldehyde addition strategy to rapidly prepare triene **36**, an early intermediate in their total synthesis of curacin A (Scheme 7).[67] Hydrozirconation of alkyne **34** and transmetalation with Et_2Zn was followed by addition of tiglic aldehyde to the reaction mixture, and then the expected allylic alcohol was immediately oxidized to the corresponding ketone **35**, isolated in 85% overall yield. Pd(0)-catalyzed Bu_3SnH reduction of the triflate formed by trapping of the kinetic enolate afforded the all-*trans*-triene **36** in 71% yield. A similar sequence was used to prepare the all-(*E*)-polyene fragments of asukamycin[68] and nisamycin.[69]

Williams and co-workers have used the Zr-Zn exchange methodology in their total synthesis of ratjadone (Scheme 8).[70] Construction of the 5,6-dihydropyran-2-one was initiated by addition to aldehyde **38** of the alkenylzirconocene prepared from alkyne **37**. Allylic alcohol **39** was isolated as a 1:1 mixture of diastereomers in very high yield. To set the stereochemistry of the newly formed stereocenter, the alcohol was oxidized and the resulting enone immediately subjected to an assymetric reduction, which gave a 5:1 mixture of diastereomers.



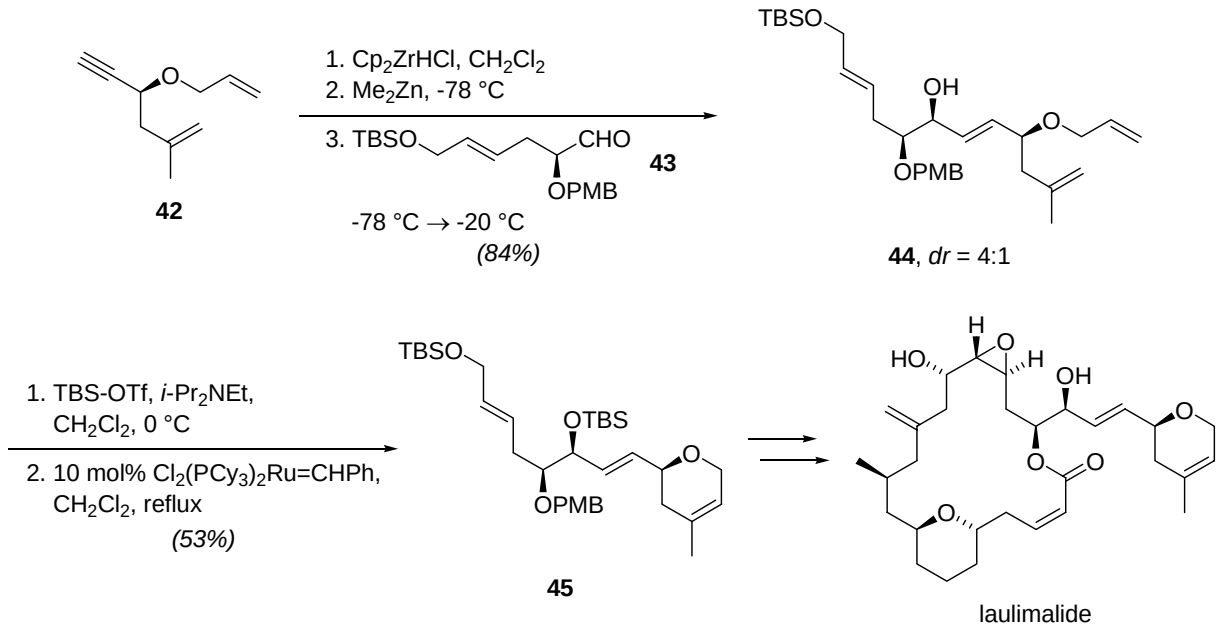
Scheme 7. Zr-Zn transmetalation/aldehyde addition in Wipf's total synthesis of curacin A.



Scheme 8. Zr-Zn transmetalation/aldehyde addition in Williams' total synthesis of ratjadone.

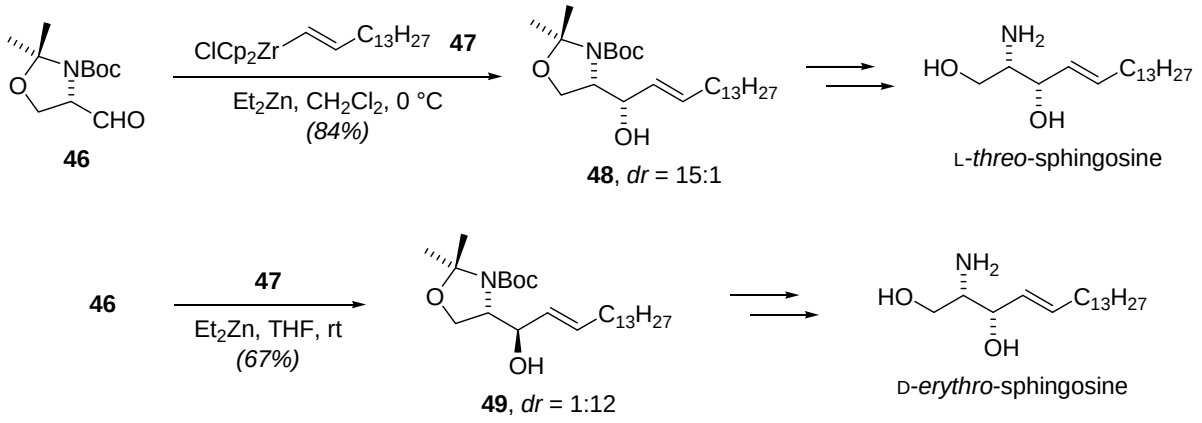
Williams and co-workers again used this methodology in their total synthesis of laulimalide (Scheme 9).[71] To set the desired C_{20} stereocenter, a chelation-controlled addition to aldehyde **43** of the alkenylzinc reagent, derived from hydrozirconation of alkyne **42** and trans-metalation with Me_2Zn, was used. The desired allylic alcohol **44** was obtained as a 4:1 mixture of diastereomers. The next step in their sequence involved another popular organometalic reaction of alkenes, namely a ring-closing metathesis. The one-pot Zr-Zn transmetalation protocol was preferable in this case to addition of an alkenylzincate reagent, which required preparation and isolation of the corresponding vinyl iodide, then lithium-halogen exchange with

t-BuLi, and finally transmetalation with Me_2Zn. Though the addition of this zincate gave a higher diastereoselectivity, the Zr-Zn transmetalation/aldehyde addition protocol was considered more practical. The same zincate strategy was earlier used to form the same C_{20} stereocenter, using very similar substrates, by Messenger and Davidson.[72] Through the diastereoselectivity of the addition was very high (only one stereoisomer was obtained), the yield was low (45%) and the reaction mixture was contaminated with 15% of a difficult to separate by-product resulting from methyl addition to the aldehyde.



Scheme 9. Zr-Zn transmetalation/aldehyde addition in Williams' synthesis of laulimalide.

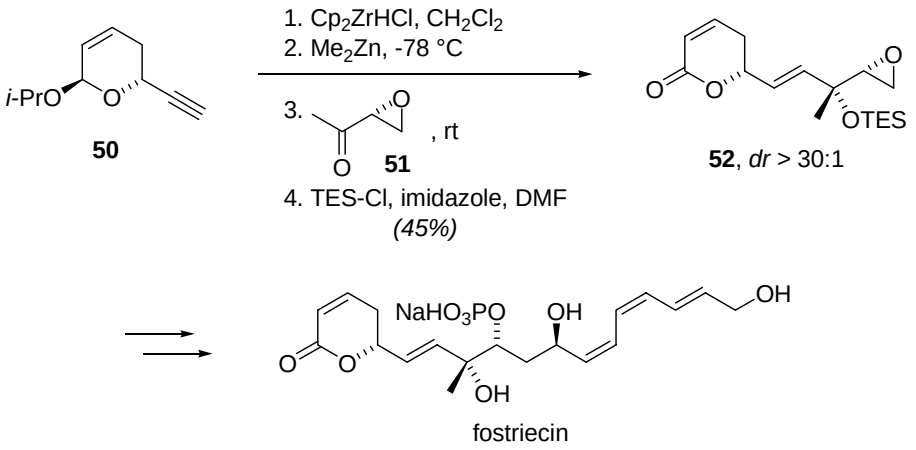
Murakami and Furusawa used the Zr-Zn methodology to prepare both *erythro*- and *threo*-sphingosine, using a highly diastereoselective addition of alkenylzirconocene **47** to Garner's aldehyde (**46**) in the presence of Et_2Zn (Scheme 10).[73] Interestingly, the choice of solvent used for the reaction dictated the relative stereochemistry of the allylic alcohol product. In CH_2Cl_2, the *syn*-alcohol **48** was formed in high diastereoselectivity and high yield. However, keeping all other conditions identical but performing the entire one-pot reaction in THF, *anti*-alcohol **49** was favored with a diastereoselectivity of 12:1 and an isolated yield of 67%. An improved yield of 70% and a selectivity of 20:1 was achieved by using half an equivalent of $ZnBr_2$ instead of one equivalent of Et_2Zn.



Scheme 10. Zr-Zn transmetalation/aldehyde addition in the diastereoselective synthesis of sphingosines.

Chavez and Jacobsen extended the Zr-Zn methodology to the addition to ketones, specifically epoxyketone **51**.[74] Their total synthesis of fostriecin required a diastereoselective, chelation-controlled vinylation of enantiomerically pure **51** (Scheme 11). The most successful model study was hydrozirconation of 1-octyne, transmetalation with Me_2Zn and addition to **51**, which afforded the expected tertiary allylic alcohol with a diastereoselectivity of >30:1 and in 75% isolated yield. Using alkyne **50** in place of 1-octyne also afforded the desired allylic alcohol (isolated as TES-ether **52** in 45% combined overall yield) with >30:1 diastereo-selectivity. The Zr-Zn methodology has also been extended to α-ketoesters by Wipf and Stephenson.[75]

Unsuccessful use of this methodology has been reported in stereocontrolled additions to *in situ* formed oxacarbenium ions (due to competitive alkyl group transfer)[76] and in studies towards the nautral products halicholactone,[77] constanolactone A,[78] and macrolactin A.[79] In the latter synthesis, a late-stage hydrozirconation of enyne **54**, transmetalation to Me_2Zn, and addition to aldehyde **53** was planned (Figure 2). Though a test addition to benzaldehyde did afford the desired 1,2-addition product in 50% yield, no addition to aldehyde **53** was observed and the approach was abandoned.



Scheme 11. Zr-Zn transmetalation/ketone addition in Jacobsen's total synthesis of fostriecin.

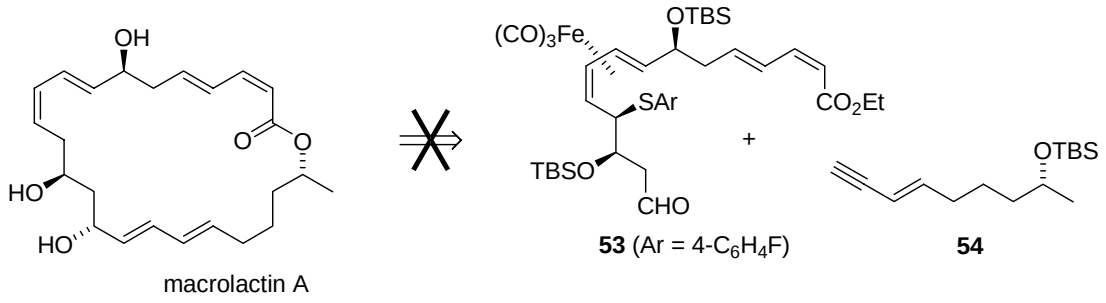
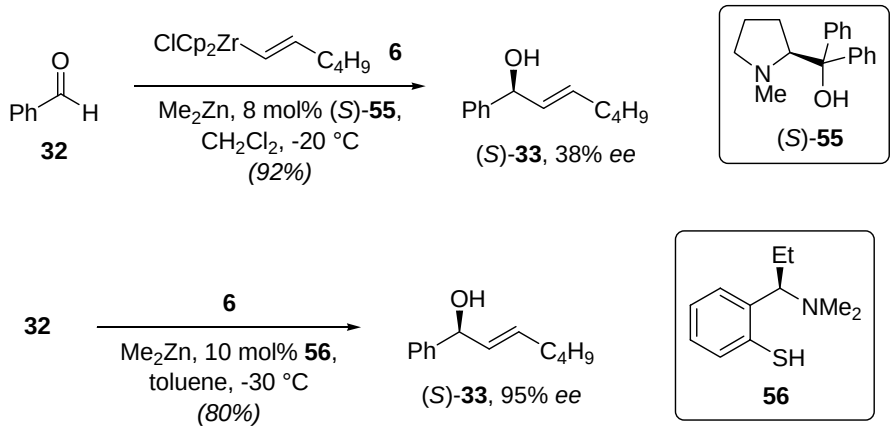


Figure 2. Unsuccessful Zr-Zn transmetalation/aldehyde addition in an attempted total synthesis of macrolactin A.

In their initial communication on the Zr-Zn transmetalation/aldehyde addition methodology, Wipf and Xu reported that performing the reaction detailed in Scheme 6 in the presence of 8 mol% of proline-derived ligand **55** and at -20 °C afforded enantiomerically enriched allylic alcohol (*S*)-**33**, though with a low *ee* of 38%. Wipf and Ribe improved the *ee* to 95% by performing the reaction at -30 °C in toluene, in the presence of 10 mol% of amino thiol **56** (Scheme 12).[80] Critically, the process also required a 60 min incubation, at -30 °C, of the zirconocene/Me_2Zn/chiral ligand mixture prior to addition to the electrophile. Without this added step, which was believed to allow for complete solvation of the chiral ligand, the *ee*'s of the reaction product were not reproducible.[81] The amino thiol ligand **56** gave generally moderate to high *ee*'s for all substrates tested, including electron-rich aromatic aldehydes and aliphatic aldehydes (63-74% *ee*), and benzaldehyde and more electron-deficient aromatic aldehydes (83-

99% *ee*). When performed in the presence of amino thiol **56**, the reaction *ee* displayed a strong, positive non-linear effect.[82]

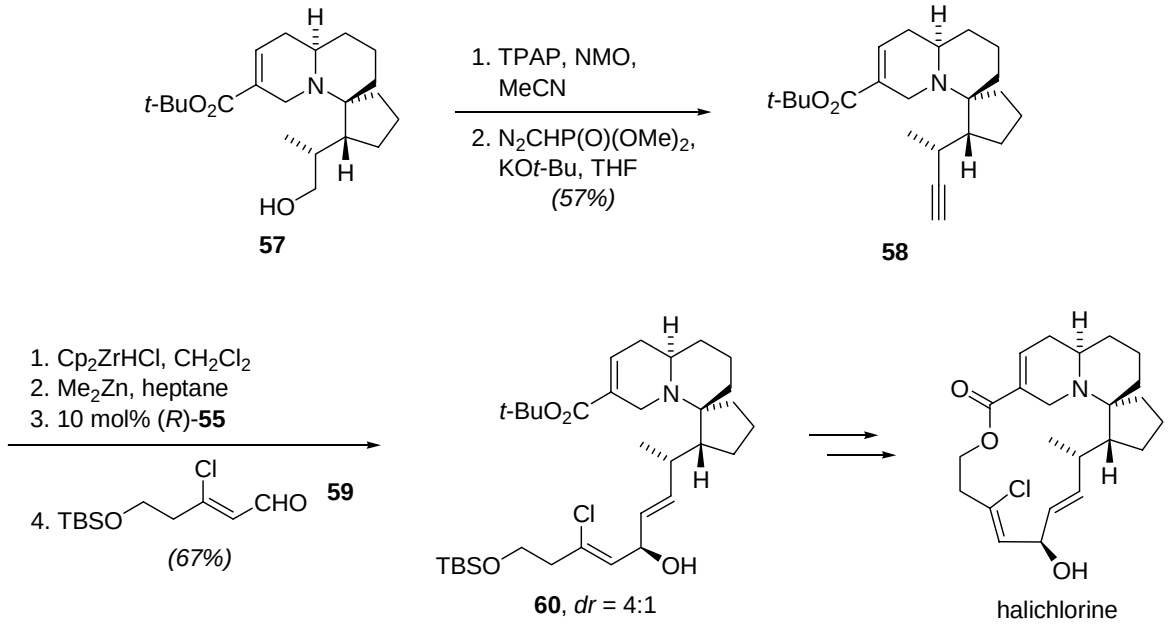


Scheme 12. Catalytic asymmetric Zr-Zn transmetalation/aldehyde addition.

The catalytic asymmetric Zr-Zn transmetalation/aldehyde addition has been used in several natural product total syntheses. Danishefsky and Trauner used this reaction at a very late stage of their total synthesis of halichlorine (Scheme 13).[83] Since Horner-Wadsworth-Emmons homologation of the aldehyde prepared by oxidation of alcohol **57** was unsuccessful, alkyne **58** was instead prepared and used in an asymmetric vinylation of aldehyde **59**, catalyzed by amino alcohol **55**. The desired bis-allylic alcohol **60** was isolated in 67% yield as a 4:1 mixture of diastereomers. In the absence of ligand **55**, the ratio of diastereomers was 1:1. Completion of the total synthesis required only protection of the newly formed allylic alcohol, deprotection of the primary alcohol and ester and their subsequent coupling under Keck macrolactonization conditions, and a final deprotection.

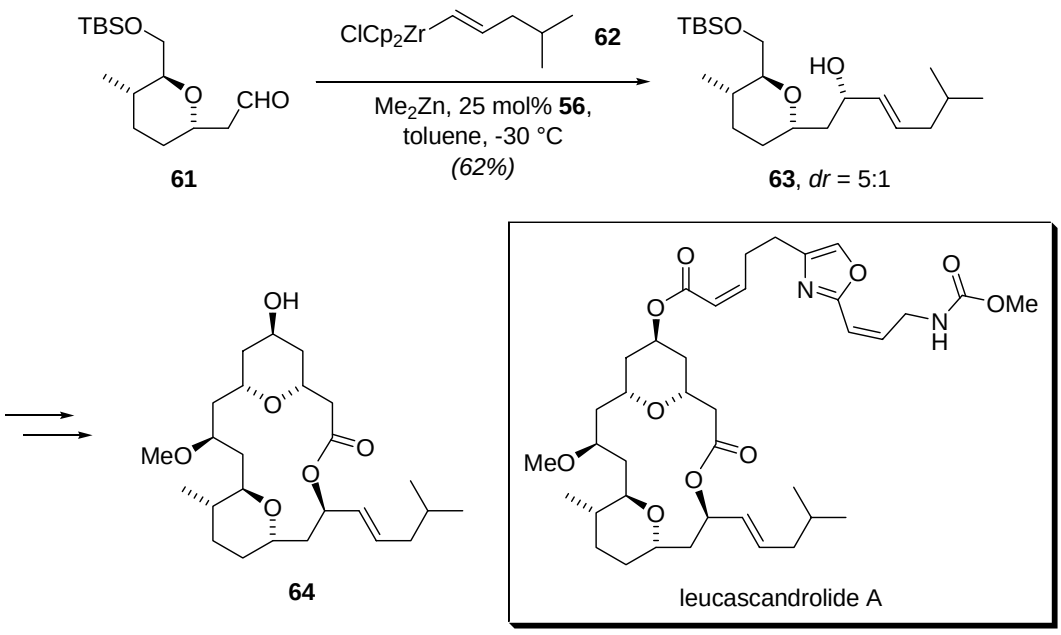
Wipf and Reeves used this asymmetric methodology in their formal synthesis of leucascandrolide A (Scheme 14).[84] The zirconocene **62** was added to aldehyde **61** in the presence of Me_2Zn and 25 mol% of amino thiol **56**. Allylic alcohol **63** was isolated in 62% yield as a 5:1 mixture of diastereomers, though the major diastereomer had a configuration at the new alcohol stereocenter that was opposite to that predicted. This forced a change in strategy for completion of the macrocyclic core. In the absence of an external chiral ligand, the Me_2Zn-mediated alkenylzirconocene addition to aldehyde **61** afforded a 1.8:1 mixture of diastereomers.[85]

Williams and co-workers also used the Zr-Zn methodology to construct the same C-C bond in their approach to leucascandrolide A, though as with their approach to ratjadone (Scheme 8), no chiral ligand was employed and the newly formed allylic alcohol was immediately oxidized and then stereoselectively reduced.[86]

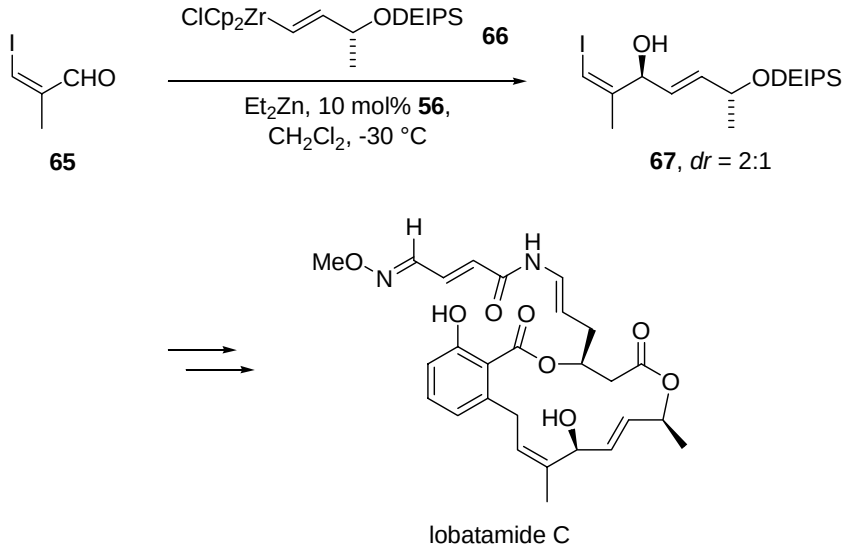


Scheme 13. Catalytic asymmetric Zr-Zn transmetalation/aldehyde addition in Danishefsky's total synthesis of halichlorine.

Porco and co-workers used the asymmetric Zr-Zn transmetalation/aldehyde addition in their total synthesis of lobatamide C (Scheme 15).[87] Again, amino thiol **56** was used in catalytic quantities (10 mol%), here to affect the Et_2Zn-mediated addition of alkenylzirconocene **66** to aldehyde **65**. The desired allylic alcohol was isolated in 68% yield but only as a 2:1 mixture of diastereomers, however, other methods evaluated for setting this stereocenter, including lipase reduction, asymmetric reduction of the corresponding dienone, and catalytic asymmetric alkynylation of the aldehyde, were no more effective. In the absence of **56**, the alcohol **67** was isolated in 87% yield as a 1:1 mixture of diastereomers.



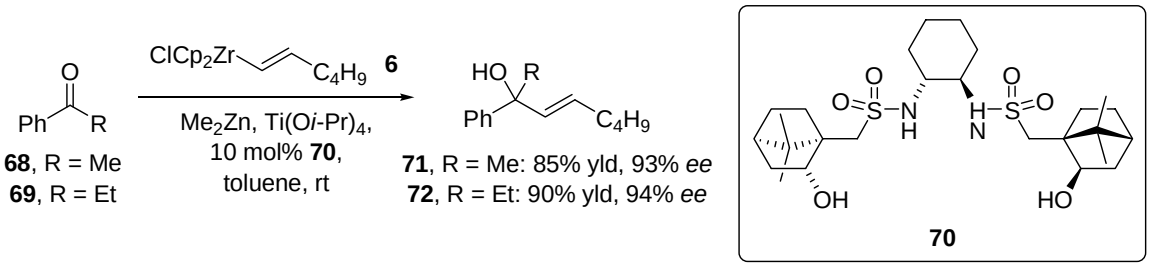
Scheme 14. Catalytic asymmetric Zr-Zn transmetalation/aldehyde addition in Wipf's total synthesis of leucascandrolide A.



Scheme 15. Catalytic asymmetric Zr-Zn transmetalation/aldehyde addition in Porco's total synthesis of lobatamide C.

Li and Walsh have recently reported the catalytic asymmetric vinylation of ketones using the Zr-Zn transmetalation strategy (Scheme 16).[88] Though Walsh and co-workers had previously reported a catalytic asymmetric vinylation of aldehydes using a B-Zn transmetalation/aldehyde

addition,[89] in the presence of the chiral amino alcohol (-)-MIB,[90] a different approach was required for ketones. High levels of enantiocontrol were achieved using Zr-Zn transmetalation and catalytic quantities of the chiral Ti complex prepared from Ti(O*i*-Pr)$_4$ and diol **70**.[91] Under these conditions, tertiary alcohols were formed in high yield (84-98%) and with good *ee* (79-97%). For example, vinylation of acetophenone (**68**) with alkenylzirconocene **6** in the presence of stoichiometric Me_2Zn and Ti(O*i*-Pr)$_4$, and catalytic diol **70**, afforded tertiary allylic alcohol **71** in 85% isolated yield with an *ee* of 93% (the absolute stereochemistry was not determined). The analogous vinylation of propiophenone (**69**) afforded alcohol **72** in 90% yield and 94% *ee*. Other ketones succesfully tested included various arene-substituted acetophenones, 4-methyl-2-pentanone, and a few α,β-unsaturated ketones.



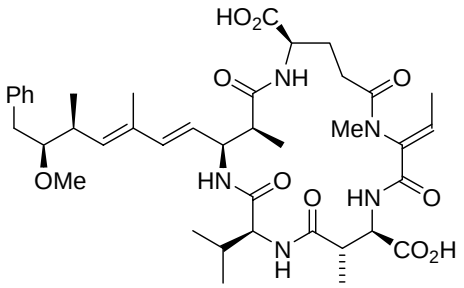
Scheme 16. Catalytic asymmetric Zr-Zn transmetalation/ketone addition.

The goal of the research presented here was to develop an asymmetric synthesis of allylic amines by extending the Zr-Zn transmetalation methodology to imines. Though an obvious disconnection, the 1,2-addition of functionalized organometallic reagents to imines has not been widely exploited for the synthesis of allylic amines. An asymmetric synthesis of α-chiral benzylamines (by addition to benzaldimines) would produce valuable building blocks which could be used to prepare analogues of ligand **56** and improve the asymmetric allylic alcohol synthesis detailed in Scheme 12.

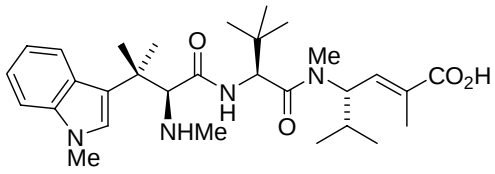
1.3. Allylic Amines

Allylic amines are important chiral intermediates in organic synthesis, for example in the preparation of unnatural amino acids.[92] This moiety is found in such natural products as

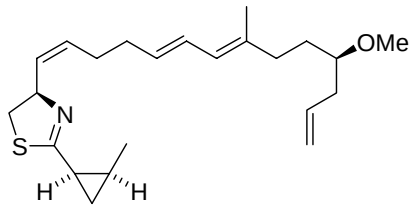
motuporin,[93] hemiasterlin,[94] cyclotheonamide B,[95] and curacin A,[96] and is also used as a peptide isostere.[97] As such, the preparation of allylic amines has long received considerable attention from the synthetic community.[98]



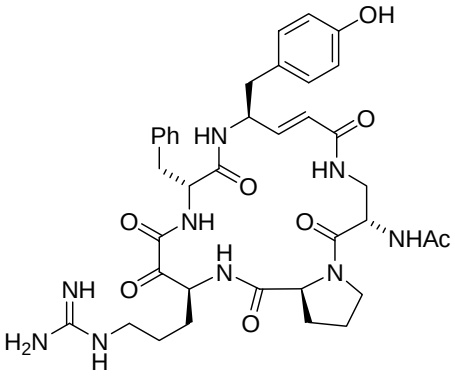
motuporin



hemiasterlin



curacin A

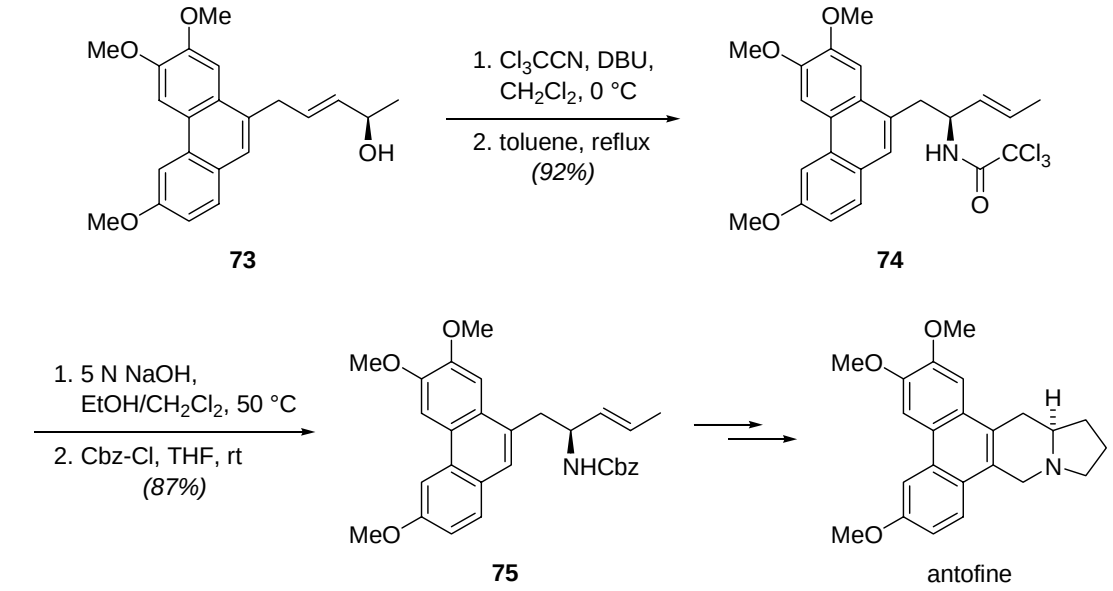


cyclotheonamide B

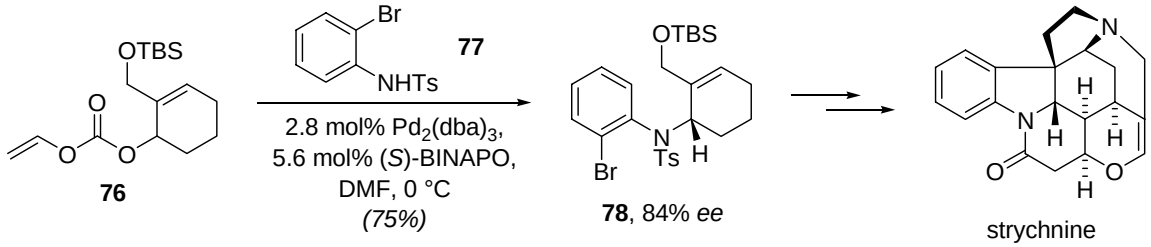
Though chiral allylic amines have been traditionally prepared by olefination of amino aldehydes,[-,99] this approach suffers from the low stability and ease of epimerization of the aldehydes. The most used modern method for the preparation of allylic amines is the Overman rearrangement.[,100] This process is a [3,3]-sigmatropic rearrangement, without loss of stereochemical integrity, of allylic imidates into allylic trichloroacetamides. A recent demonstration of the methodology was reported in the asymmetric total synthesis of antofine by Kim and coworkers (Scheme 17).[101] Chiral allylic alcohol **73** was converted into allylic amide **74** under standard Overman rearrangement conditions. Due in part to the relatively harsh conditions needed to deprotect the trichloroacetamide formed, alternate [3,3]-processes continue to be explored, including rearrangements of allyl cyanates,[102] phosphorimidates[103] and phospholidines.[104] Significantly, the metal-catalyzed preparation of enantiomerically enriched allylic amines from racemic imidates has been achieved[105] and continues to be improved.[106]

The most developed catalytic asymmetric preparation of allylic amines are allylic aminations of π-allyl complexes, pioneered by Trost.[107] A recent demonstration of this methodology was reported by Nakanishi and Mori as the first key step in their asymmetric total synthesis of strychnine (Scheme 18).[108] Allylic carbonate **76** was aminated by sulfonamide **77**

via its chiral π-allyl Pd-complex, affording allylic sulfonamide **78** in 75% yield with an *ee* of 84%. Though this transformation has not been as extensively used by the synthetic community as the Overman rearrangement, the methodology continues to be developed.[109]



Scheme 17. An Overman rearrangement in the total synthesis of antofine by Kim *et al*.



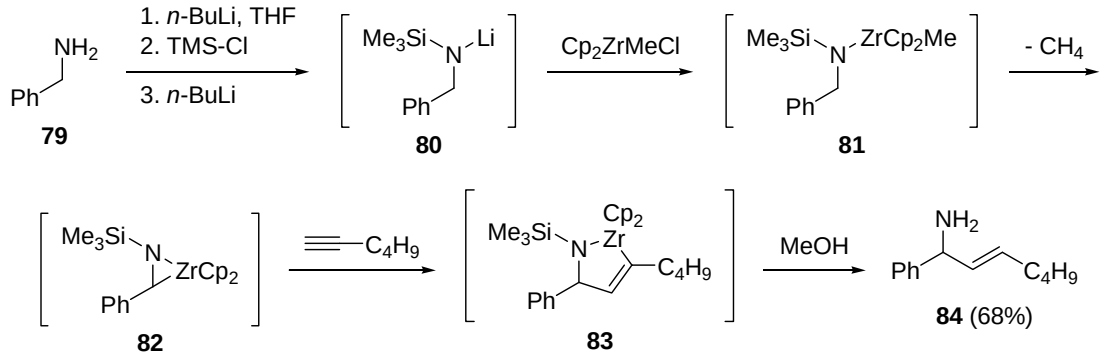
Scheme 18. Asymmetric allylic amination in Mori's total synthesis of strychnine.

Two other catalytic asymmetric preparations of allylic amines that have recently been described are Ni(II)-catalyzed hydroamination of dienes,[110] and the aza-Baylis-Hilman reaction, using the modified cinchona alkaloid β-isocepeidine.[111] Several methods have been reported for the preparation of chiral allylic amines from non-racemic precursors, including nucleophilic displacement of allylic bromides;[112] tellurium-mediated reductive opening of aziridine methanol derivatives[113] and the closely related indium-mediated opening of 2-iodo-methyl aziridines;[114] deoxygenation of 3-amino-1,2-diols;[115] and dehydration of β-hydroxy-γ-amino sulfones.[116] The

lipase[117] or chiral acid[118] mediated resolution of racemic primary allylic amines has also been used to prepare enantiomerically pure allylic amines.

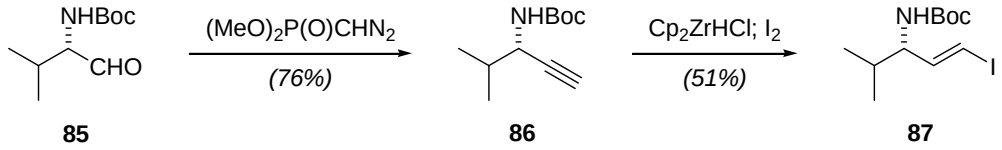
The 1,2-addition of alkenylorganometallic reagents to imines has not been widely exploited as a general method for the preparation of allylic amines.[119] One reason could be dimerization of the alkenylorganometallic reagent resulting in α-selective crotylation.[120] Many examples of catalytic asymmetric[121] and diastereoselective[122] additions of vinyllithium or vinyl Grignard reagent to imines and imine derivatives have been reported, though these are usually simply scope of a particular nucleophilic addition methodology. A number of examples of diastereoselective additions of a highly substituted alkenyllithium to sulfonylimines were reported by Braun and Opdenbusch; however, the allylic double bonds were immediately oxidatively cleaved to form amino acids.[123] In some cases, diastereoselective addition of nucleophiles to imines for the preparation of analogues of ligands,[124] peptides,[125] sugars,[126] or the antibiotic anisomycin,[127] included one example of addition of vinyllithium or vinyl Grignard. Diastereoselective addition of vinylmagnesium bromide to a chiral α-hydroxy imine was a key step in the total synthesis of 4a,5-dihydrostreptazolin,[128] and diastereoselective addition of vinyl-lithium to a chiral oxime ether was the key step in the synthesis of CP-99,994.[129] A related preparation of allylic amines, by catalytic asymmetric[130] or diastereoselective[131] 1,2-addition of nucleophiles to α,β-unsaturated imines, has been reported. Very few examples of racemic[132] or asymmetric[133] additions of vinylzinc reagents to imines have been reported.

Buchwald and co-workers have reported a zirconocene-mediated synthesis of allylic amines starting from alkynes and imines (Scheme 19).[134] Lithiation of amine **80** and addition to $Cp_2ZrMeCl$ afforded, after loss of methane, azazirconacyclopropane **82**. Coupling of **82** with alkynes such as 1-hexyne formed allylic amines such as **84** after methanolysis of the Zr-C and Zr-N bonds. The regioselectivity of alkyne coupling was excellent if one of the substituents in the 3- or 5-position of azazirconacyclopentene **83** was aromatic. Yields ranged from 48 to 80% with examples of primary aliphatic and benzylic amines, and both terminal and internal alkynes. An asymmetric, auxiliary-based variant was subsequently reported.[135] Whitby,[136] Mori,[137] and others[138] have expanded this methodology, and the equivalent Ta-[139] and Ti-mediated[140] transformations have been reported.



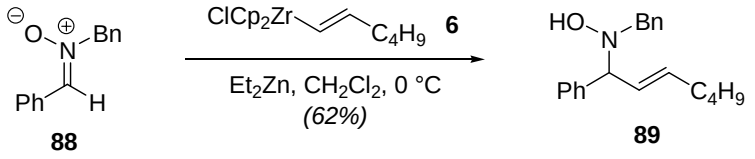
Scheme 19. Buchwald's Zr-mediated synthesis of allylic amines.

Another synthesis of allylic amines involving zirconium was reported by Hauske and co-workers (Scheme 20).[141] Non-racemic propargylic amines were prepared and then the triple bond was hydrozirconated and functionalized *via* iodination or Ni(II)-catalyzed 1,4-addition. For example, valine-derived propargyl carbamate **86** was converted into vinyl iodide **87** in modest yield. To demonstrate the scope of this transformation, seven simple amino acid derivatives were selected. The derivatized allylic amines were isolated in only 20-54% yield.



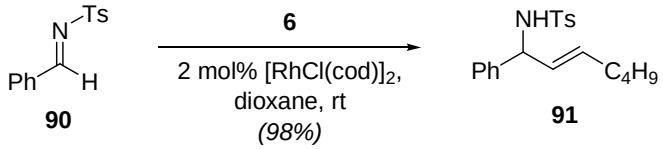
Scheme 20. Hydrozirconation of propargylic amines to form allylic amines.

A few methods for the construction of allylic amines using alkynes and imines, related to the research presented herein, have recently been reported. The Zr-Zn transmetalation strategy described in the previous section was extended by Vallée and co-workers to the preparation of allylhydroxylamines, using nitrones as electrophiles (Scheme 21).[142] For example treatment of nitrone **88** with hexenylzirconocene **6** in the presence of Et_2Zn afforded hydroxylamine **89** in 62% yield. Both aliphatic and aromatic nitrones were used in this process. The isolated yields for unfunctionalized, terminal and internal alkynes were in the range of 29-83%, whereas yields for functionalized alkynes ranged from 5-60%. The same transformation using hydroboration in place of hydrozirconation was subsequently reported.[143]



Scheme 21. Et_2Zn-mediated addition of alkenyl zirconocenes to nitrones.

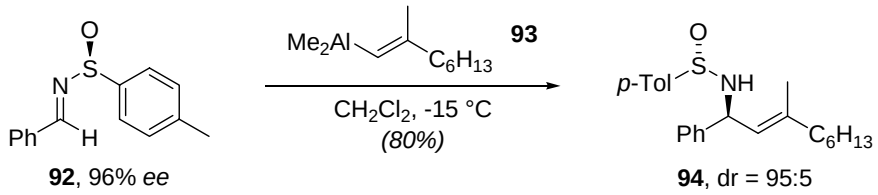
A Rh(I)-catalyzed addition of alkenyl zirconocenes to *N*-tosyl aldimines was reported by Kakuuchi, Taguchi and Hanzawa (Scheme 22).[144] For example, addition of hexenylzirconocene **6** to aldimine **90** in the presence of 2 mol% of the rhodium catalyst afforded sulfonamide **91** in near quantitative yield. The authors suggest a transmetalation of the alkenyl group from Zr to Rh prior to 1,2-addition to the aldimine. They observed no alkyl group transfer from substrates prepared by hydrozirconation of alkenes. The hydrozirconation step was performed in CH_2Cl_2 and then the solvent switched to dioxane prior to addition of the aldimine and Rh(I) catalyst to the reaction mixture. Both aromatic and aliphatic aldimines as well as functionalized alkynes all formed the desired sulfonamides in high (58-99%) yield.



Scheme 22. Rhodium(I)-catalyzed addition of alkenyl zirconocenes to imines.

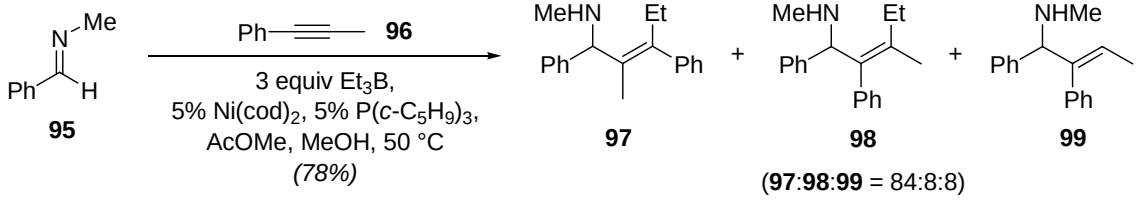
Water-accelerated carboalumination of alkynes is another effective method for the preparation of reactive alkenyl organometallics.[145] Wipf, Nunes and Ribe showed that direct addition of vinyl alanes to enantiopure *N*-sulfinimines[146] afforded trisubstituted allylic amines in high yield and good diastereoselectivity (Scheme 23).[147] For example **93**, the methylaluminated product derived from 1-octyne, was added to sulfinimine **92** affording sulfinamide **94** with an 80% isolated yield and diastereomeric ratio of 20:1. Functional group tolerance on the alkyne segment is not as broad for carboalumination as for hydrozirconation, nevertheless a range of unfunctionalized alkynes were used as well as a triisopropylsilyl ether-substituted terminal alkyne. Aromatic, cinnamyl and cyclohexyl sulfinimines were used as substrates, with isolated

yields ranging from 65-85%, and all diastereoselectivities were at least 6:1. An alkyne carbocupration, imine-addition strategy has also been used to prepare allylic amines.[148]



Scheme 23. Diastereoselective addition of alkenyl alanes to sulfinimines.

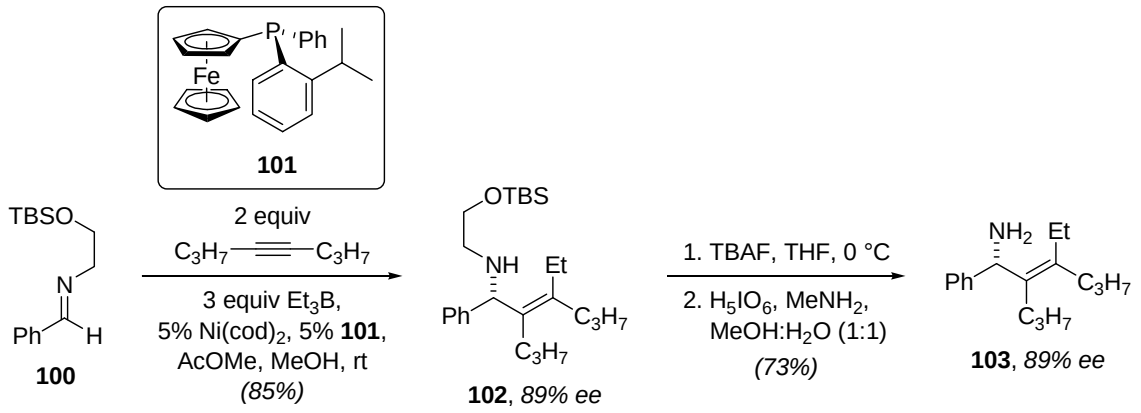
A three-component Ni(0)-catalyzed coupling of alkynes, organoboron reagents, and aldimines, forming tetrasubstituted allylic amines, was reported by Patel and Jamison (Scheme 24).[149] For example the reaction of alkyne **96**, benzaldimine **95**, and triethylborane, catalyzed by 5 mol% of a Ni(0)/trialkylphosphine complex afforded allylic amines **97-99** in 78% combined yield. The scope of this reaction was limited to internal alkynes and the regioselectivity of the double bond formed was high (9:1) only for alkyne substrates that included one aryl and one alkyl substituent. When trialkylboranes were used, the reductive coupled product **99** was formed in *ca*. 10% yield; however, when boronic acids were used, only the alkylative coupled products (for example regioisomers **97** and **98**) were isolated. Both aromatic and aliphatic aldimines were used and the isolated yields of the product mixtures ranged from 30-98%.



Scheme 24. Racemic Ni-catalyzed reductive coupling of alkynes, boranes, and imines.

Recently, this reaction was extended to an asymmetric synthesis of allylic amines by using chiral phosphine **101** and alkylimines such as **100** (Scheme 25).[150] Not only were most of the desired allylic amines obtained in good yield (42-95%) and high enantioselectivity (51-89% *ee*), but the undesired products of reductive coupling, such as **99**, were avoided under these

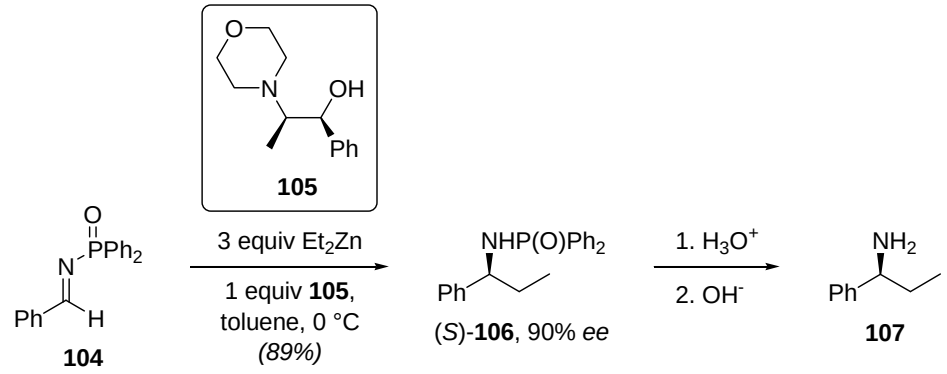
reaction conditions. The enantioenriched allylic amines formed were oxidatively deprotected with no loss of enantiomeric purity to afford the corresponding primary amines. No explanation for determination of the absolute stereochemistry of the allylic amines was given.



Scheme 25. Asymmetric Ni-catalyzed reductive coupling of alkynes, boranes, and imines.

1.4. Diethylzinc Additions to Aldimines

Despite the vast body of knowledge for dialkylzinc (R_2Zn) additions to aldehydes,[151] the corresponding addition to aldimines has not been as widely studied due to their significantly lower electrophilicity.[152] Most examples have been limited to the addition of strongly basic reagents such as Grignard reagents or alkyllithiums. Katritzky and Harris reported the asymmetric addition of Et_2Zn to *N*-(amidobenzyl)-benzotriazoles (masked *N*-acylimines) in up to 76% *ee* in the presence of one equivalent of *N*,*N*-dibutylnorephedrine.[153] Soai and co-workers soon afterwards reported that *N*-diphenylphosphinoylimines such as **104** were sufficiently active for R_2Zn addition, and the easily deprotected phosphinamide products **106** could be prepared in up to 90% *ee* and recrystallized to higher enantiomeric purities (Scheme 26).[154] Again, one equivalent of a norephedrine ligand was used. Similar levels of enantiocontrol (84% *ee* and 76% isolated yield) were obtained when the same reaction was performed in neat Et_2Zn.[155]



Scheme 26. Soai's asymmetric addition of Et_2Zn to *N*-diphenylphosphinoylimine **104**.

Soai has subsequently developed polymer-[156] and dendrimer-supported[157] norephedrine ligands for use in this asymmetric transformation, and other groups have developed amino alcohols **108**,[158] **109**,[159] **110**,[160] **111**,[161] **112**,[162] and **113**.[163] A survey of results is presented in

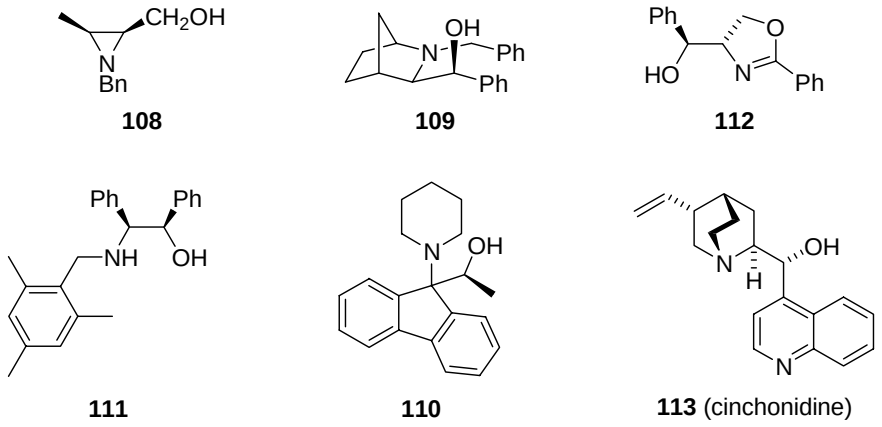
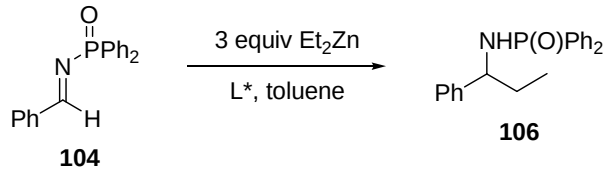


Table 1. The isolated yields of **106** were in general high, normally within the range of 65-90%, and the reaction required at least three equivalents of Et_2Zn. Highest *ee* was achieved when one equivalent of the chiral ligand was used (compare Entries 1 with 2; 3 with 4; 5 with 6; and 10 with 11 and 12). The reaction times were long and usually required room temperature for acceptable rates. Pericàs and co-workers developed an amino alcohol/silyl halide protocol that allowed performing the reaction at -20 °C, though no significant improvement in yield or *ee* was observed with the asymmetric ligands tested (Entry 7). Recently, Beresford has found that using catalytic quantities of the natural alkaloid cinchonidine (**113**) as the amino alcohol and two equivalents of MeOH afforded α-ethylbenzylamine **106** with a similar yield and *ee* (entry 13) as when one equivalent of **113** was used (entry 10).

Table 1. Representative examples for asymmetric Et_2Zn addition to **104**.

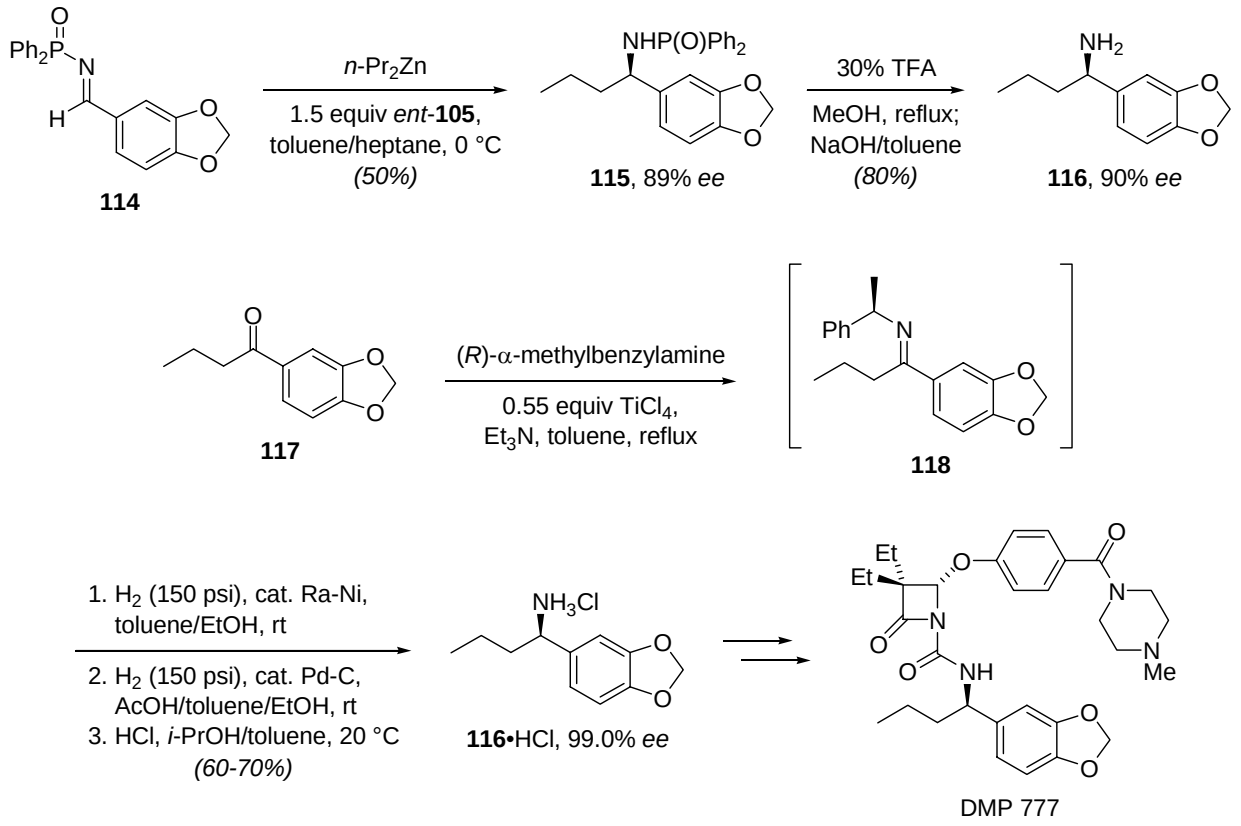


104 **106**

Entry	L* (Equiv)	Temperature	Yield (%)	ee (%)	Reference
1	**105** (1.0)	0 °C	89	90 (*S*)	154
2	**105** (0.5)	0 °C	69	85 (*S*)	154
3	**108** (1.0)	rt	63	94 (*R*)	158a
4	**108** (0.5)	rt	76	87 (*R*)	158a
5	**109** (1.0)	rt	75	97 (*S*)	159c
6	**109** (0.5)	rt	68	92 (*S*)	159c
7[a]	**110** (1.0)	-20 °C	75	92 (*S*)	160b
8[b]	**111** (1.0)	rt	92	97 (*R*)	161b
9[b]	**112** (1.0)	rt	77	91 (*S*)	162a
10[c]	**113** (1.0)	rt	76	93 (*R*)	163a
11[c]	**113** (0.5)	rt	77	87 (*R*)	163a
12[c]	**113** (0.05)	rt	50	69 (*R*)	163b
13[c]	**113** (0.2)[d]	rt	70	93 (*R*)	163b

[a]1 equiv TIPS-Cl added to the reaction mixture. [b]5 equiv Et_2Zn used. [c]12 equiv Et_2Zn used. [d]2 equiv MeOH added.

The process chemistry group at Bristol-Myers Squibb tested the asymmetric alkylation of *N*-diphenylphosphinoylimines during the large-scale synthesis of a candidate for the treatment of cystic fibrosis and rheumatoid arthritis, DMP 777 (Scheme 27).[164] Alkylation of imine **114** with *n*-Pr_2Zn in the presence of 1.5 equivalents of norephedrine-derived amino alcohol *ent*-**105** was performed on a 30 mmol scale, affording (*R*)-**115** in 67% conversion, but 50% isolated yield (after crystallization), and 89% *ee*. Phosphinamide **115** was then deprotected using TFA/MeOH at reflux. Ultimately, a diastereoselective hydrogenation of chiral ketimine **118** was selected to prepare large quantities of chiral amine **116**, despite destruction of the chiral auxiliary in this process. The phosphinimine alkylation method was undesirable due to the relatively low *ee* of 89% obtained, and the need to use stoichiometric quantities of *ent*-**105**.



Scheme 27. Comparison of asymmetric alkylation of *N*-diphenylphosphinoylimine **114** and diastereoselective hydrogenation by the process group at Bristol-Myers Squibb.

Tomioka and co-workers reported an asymmetric alkylation of *N*-tosylimines, catalyzed by $Cu(OTf)_2$ and phosphine **119**.[165] Several other groups have subsequently investigated this Cu-catalyzed reaction, using ligands **122**,[166] **123**,[167] **124**,[168] and **125**.[169] A survey of their results (for alkylation of imines derived from aromatic aldehydes) is shown in Table 2. Tomioka and co-workers improved their ligand's selectivity by preparing **120** (for Et_2Zn addition, entry 1) and **121** (for Me_2Zn and *i*-Pr_2Zn addition, entries 2 and 3). Charette and co-workers have developed ligand **122** for the alkylation of phosphinimines (entries 4-6), resulting in a superior process due to the significantly milder deprotection conditions of diphenylphosphinamides compared to sulfonamides. High *ee's* were reported for Et_2Zn, Me_2Zn and *i*-Pr_2Zn additions to both aromatic and *in situ* generated aliphatic imines. Hoveyda, Snapper and co-workers have successfully developed a Zr-catalyzed asymmetric addition of Et_2Zn to imines derived from condensation of aryl aldehydes and *o*-anisidine, in the presence of as little as 0.1 mol% of peptide **126** (entry

10).[170] Dahmen and Bräse have reported that *in situ* generated *N*-formylimines can be alkylated by Et_2Zn in the presence of catalytic quantities of paracyclophane amino alcohol **127** affording adducts in very high yield and enantioselectivity (entry 11).[171]

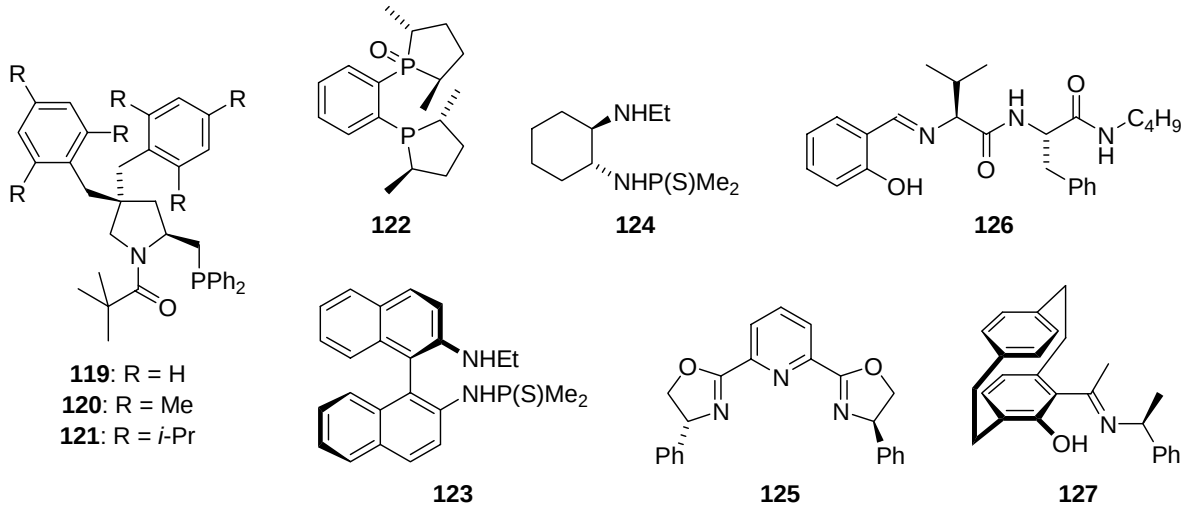
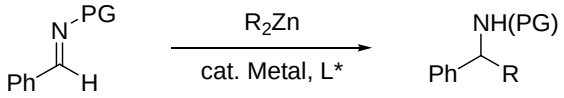


Table 2. Representative examples for catalytic asymmetric R_2Zn addition to aromatic imines.

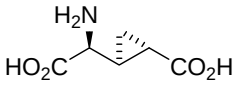


Entry	R (Equiv)	PG	Metal (mol%)	L* (mol%)	Yield (%)	ee (%)	Reference
1[a]	Et (2)	Ts	$Cu(OTf)_2$ (5)	**120** (6.5)	97	96 (*S*)	165c
2[b]	Me (8)	Ts	$Cu(OTf)_2$ (20)	**121** (15)	97	87 (*S*)	165c
3[a]	*i*-Pr (2)	Ts	$Cu(OTf)_2$ (20)	**121** (15)	92[c]	78 (*S*)	165c
4[a]	Et (2)	$P(O)Ph_2$	$Cu(OTf)_2$ (6)	**122** (3)	96	98 (*S*)	166b
5[b]	Me (3)	$P(O)Ph_2$	CuOTf (5)	**122** (5)	87	97 (*S*)	166b
6[a]	*i*-Pr (3)	$P(O)Ph_2$	$Cu(OTf)_2$ (10)	**122** (5)	84	95 (*S*)	166b
7[a]	Et (2)	Ts	$CuBF_4$ (3)	**123** (6)	93	86 (*S*)	167b
8[a]	Et (2)	Ts	$CuClO_4$ (3)	**124** (6)	92	68 (*S*)	168
9[d]	Et (4)	Ts	$Cu(OTf)_2$ (10)	**125** (12)	58	77 (*S*)	169
10[b]	Et (3)	2-C_6H_4OMe	$Zr(Oi\text{-}Pr)_4$ (20)	**126** (0.1)	82	93 (*S*)	170a
11[e]	Et (6)	CHO	none	**127** (2)	99	95 (*R*)	171

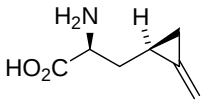
[a]Reaction in toluene at 0 °C. [b]Reaction in toluene at rt. [c]5% of BnNHTs also isolated. [d]Reaction in toluene at -20 °C. [e]Reaction in hexane at 10 °C.

1.5. Simmons-Smith Cyclopropanation

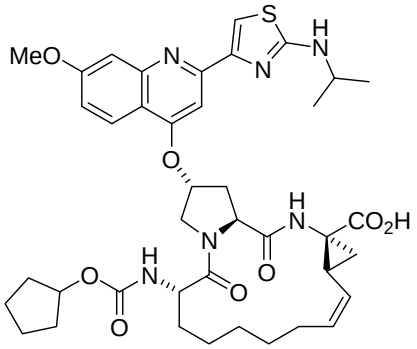
In the course of the research presented here, a one-pot imine vinylation/cyclopropanation was discovered. The mechanism was thought to involve an allylic amide-directed Simmons-Smith cyclopropanation.[172] Cyclopropane amino acids are of considerable interest as many, such as (2*S*,1'*S*,2'*S*)-2-(carboxycyclopropyl)glycine (L-CCG-I)[173,174] and (2*S*,4*R*)-hypoglycin A,[175] show biological activity.[176] They are also increasingly used in the pharmaceutical industry, in active compounds such as BILN 206.[177]



L-CCG-I



hypoglycin A

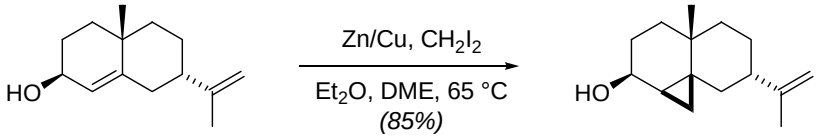


BILN 2061

Simmons and Smith discovered that the cyclopropanation of alkenes could be accomplished using the product of a zinc/copper couple and CH_2I_2.[178] The active reagent was believed to be the electrophilic zinc carbenoid $IZnCH_2I$. Furukawa and co-workers found that a similar cyclopropanating reagent, presumably $EtZnCH_2I$, could be formed by mixing Et_2Zn and CH_2I_2.[179] A number of metal/CH_2X_2 (X = halogen) combinations, with or without additional ligands, have been subsequently developed.[b,180]

The Simmons-Smith reaction has gained wide use for the cyclopropanation of alkenes due to its tolerance of most common functional groups including alkynes, alcohols, ethers, aldehydes, ketones, and carboxylic acids and their derivatives. Dihalides other than CH_2I_2, such as CH_3CHI_2, can be used to form trisubstituted cyclopropanes.[181] CH_2Cl_2 is the solvent of choice for this reaction, since it is "non-basic, unreactive towards the zinc reagents, and polar enough to solubilize the substrates."[a]

An important characteristic of the Simmons-Smith cyclopropanation is that it can be directed by allylic alcohols and ethers.[,182] For example, the more sterically hindered β-face of the allylic double bond of alcohol **128** was diastereoselectively and chemoselectively cyclopropanated using the Simmons-Smith reagent (Scheme 28).[183]

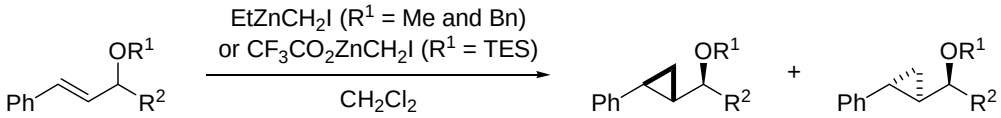


128 **129**

Scheme 28. Alcohol-directed Simmons-Smith cyclopropanation.

(*Z*)-Disubstituted and trisubstituted allylic double bonds nearly always give very high *syn*-selectivities when cyclopropanated; however, selectivities with (*E*)-disubstituted double bonds are much lower, and highly reagent- and substituent-dependant.[184] In some cases (*E*)-disubstituted allylic ethers can favor *anti*-selectivity (Table 3).[185] Two trends can be observed: as the size of R^2 increases, *syn*-selectivity increases as well; however, the size of the R^1 ether has the opposite effect, increasing *anti*-selectivity.

Table 3. Substituent effects on *syn*/*anti* selectivity for (*E*)-disubstituted allylic ethers.



Entry	R^1	R^2	Yield (%)	*syn*:*anti*	Reference
1	Me	Me	95	39:61	185a
2	Me	Et	93	77:23	185a
3	Me	*i*-Pr	94	98:2	185a
4	Bn	Me	94	10:90	185a
5	Bn	Et	97	33:67	185a
6	Bn	*i*-Pr	82	95:5	185a
7	TES	Me	87	>1:99	185b
8	TES	Et	87	3:97	185b
9	TES	i-Pr	78	30:70	185b

Transition state models that explain these trends are shown in Figure 3. The allylic $A^{1,3}$-strain of transition state **I**, normally used to explain *syn*-selectivity for allylic alcohol-directed cyclopropanation (i.e. R^1 = H for the allylic alcohol substrate), decreases relative to the strain between the R^1 and R^2 groups in transition state **II** for sufficiently large R^1 and small R^2 groups. Allylic $A^{1,3}$-strain is the dominant interaction for (*Z*)-allylic ethers.

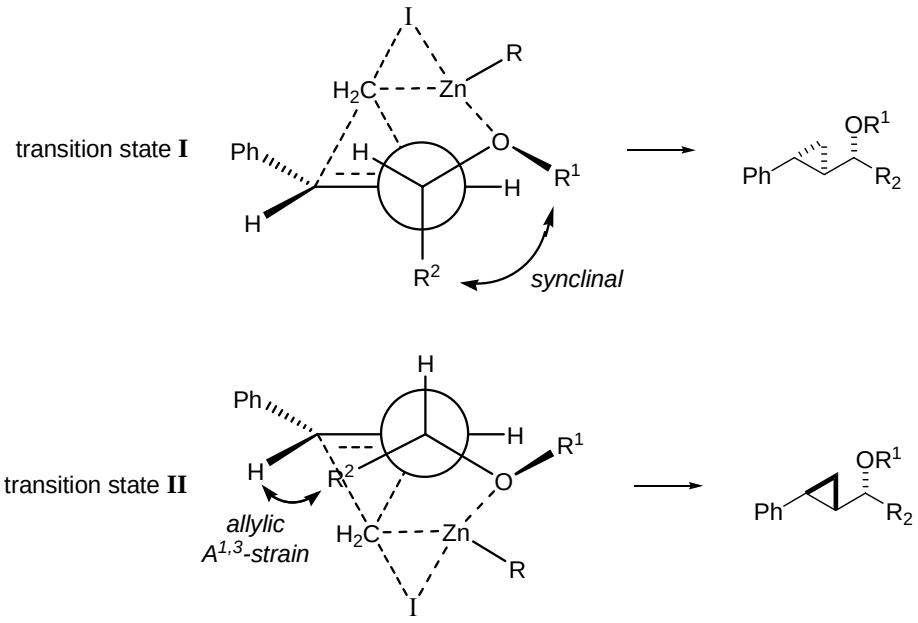
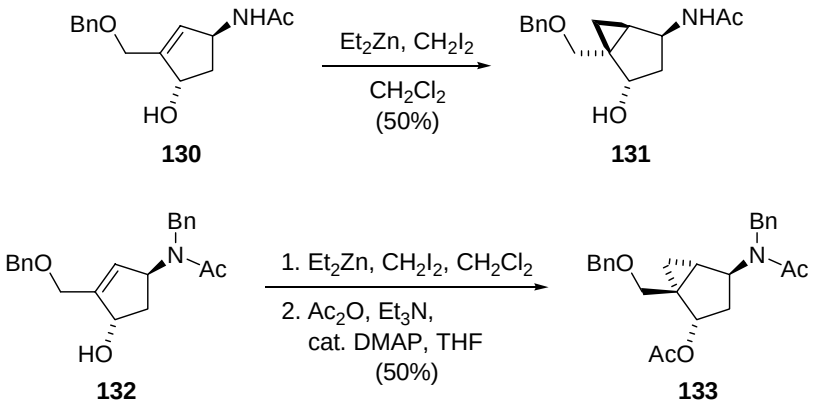


Figure 3. Transition state models for *anti*- and *syn*-selective cyclopropanations of allylic ethers.[a]

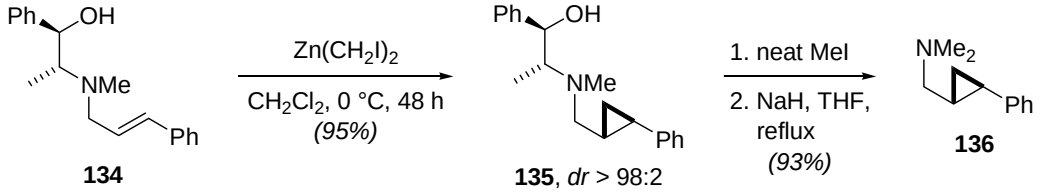
Amides can also be strong directing groups in the Simmons-Smith reaction, though there are very few published examples. Cyclopentenylamide **130** was cyclopropanated exclusively *syn* to the amide, despite the presence of an allylic alcohol on the opposite face of the ring (Scheme 29).[186] Reversal of selectivity was observed when the fully *N*-protected cyclopentene **132** was subjected to the same reaction conditions. The related cyclopropanation of α,β-unsaturated amides using SmI_2/CH_2I_2 was proposed to involve co-ordination of Sm to the carbonyl oxygen.[187]

Amines are normally not directing groups for Simmons-Smith cyclopropanation, likely due to competitive formation of zinc-complexed ammonium ylides.[188] Aggarwal and co-workers have found that a suitably proximal hydroxyl group inhibited ylide formation between allylic amines and bis-iodomethylzinc, thus allowing cyclopropanation of the alkene (Scheme 30).[189] For example, pseudoephedrine-containing allylic amine **134** was cyclopropanated to afford **135** as a single diastereomer in very high yield. Tertiary amines were required, and no additional functional groups, such as alcohols or esters, were tolerated as substituents on the substrate. The

chiral auxiliary was removed in high yield by quaternizing the amine followed by heating with NaH.



Scheme 29. Amide-directed Simmons-Smith cyclopropanation.

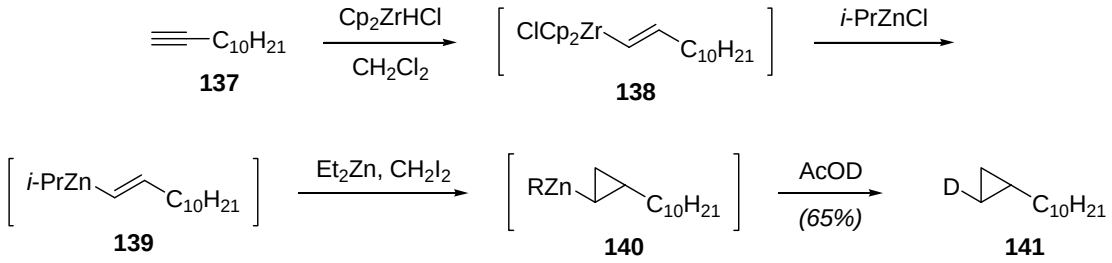


Scheme 30. Amine-directed Simmons-Smith cyclopropanation.

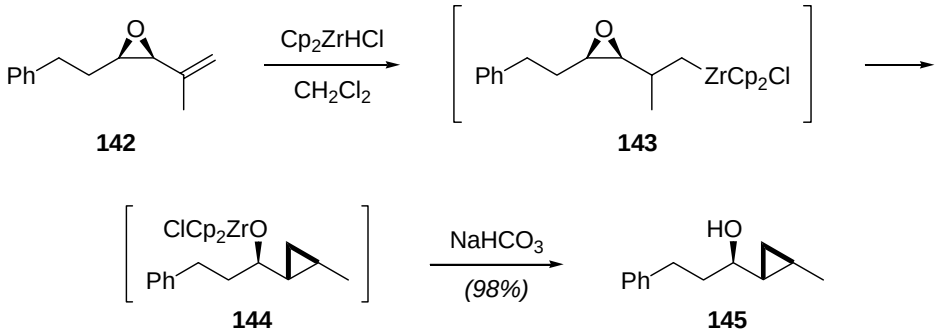
Oshima and co-workers have combined the Zr-Zn transmetalation strategy with Simmons-Smith cyclopropanation conditions for a net synthesis of *trans*-disubstituted cyclopropanes from alkynes (Scheme 31).[190] For example, hydrozirconation of 1-dodecyne and transmetalation with *i*-PrZnCl formed alkenylzinc reagent **139**. Addition of the Furukawa reagent to the reaction mixture, stirring at room temperature for 1 h, and quenching with deuterated acetic acid afforded cyclopropane **141** (*via trans*-cyclopropylzinc species **140**). Cu-mediated allylation of **140** afforded the corresponding allyl-substituted cyclopropane.

Taguchi, Hanzawa and co-workers have reported another Zr-mediated synthesis of cyclopropanes. They prepared cyclopropyl alcohols from vinyloxiranes by simply treating the substrate with Schwartz reagent in CH_2Cl_2 (Scheme 32).[191] This reaction was very diastereoselective for *cis*-vinyloxirane **142**, as *C*-cyclopropyl alcohol **145** was the only diastereomer isolated from the reaction mixture. When the *trans*-vinyloxirane was used, the diastereomeric

ratio of the *anti*,*trans*-cyclopropane (vs. *anti*,*cis*-) was 80:20. The analogous hydrozirconation of vinylaziridines afforded *C*-cyclopropylalkylamines. Allylic ethers have also been converted into cyclopropanes by the same mechanism, however, a Lewis acid was needed for deoxygenation.[192]



Scheme 31. Zr-Zn transmetation/Simmons-Smith cyclopropanation.



Scheme 32. Synthesis of *C*-cyclopropyl alcohols from vinyloxiranes using Schwartz reagent.

2. Results and Discussion

2.1. Synthesis of Allylic Amines[193]

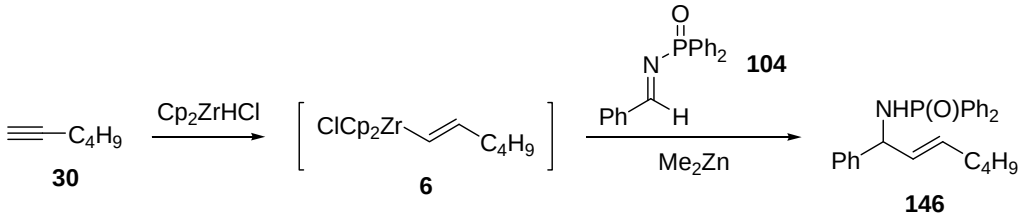
The research project described here was initiated to extend the Zr-Zn methodology developed in the Wipf group to an asymmetric synthesis of allylic amines. Optimization of a racemic transformation analogous to the allylic alcohol synthesis detailed in Scheme 6 was undertaken using 1-hexyne (**30**) and benzaldimine **104**. The hydrozirconation of terminal alkynes is very rapid in CH_2Cl_2 or THF at room temperature, thus initially the one-pot reaction was attempted in either of these two solvents (Table 4). Standard conditions were as follows: 1.5 equivalents of **30** were hydrozirconated with an equimolar quantity of Cp_2ZrHCl. Once the reaction mixture was homogeneous (~10 min), it was cooled to -78 °C, treated with 1.5 equivalents of Me_2Zn, rapidly warmed to room temperature, cannulated into a solution of aldimine **96**, and stirred until TLC analysis showed consumption of the imine. Performing the reaction under these standard conditions in CH_2Cl_2 yielded only 41% of the desired allylic amide **146** after 18 h (entry 1). The reaction time was decreased significantly by heating the reaction mixture to reflux (entry 2), though the isolated yield increased only to 59%. Increasing the number of equivalents of reagents and heating at reflux (entries 3 and 4) had a detrimental effect on the yield (*vide infra*). There was no trace of 1,2-addition in the absence of Me_2Zn in CH_2Cl_2 after 4 h (entry 5).

Under standard conditions in THF, only 54% of **146** was isolated after 36 h (Table 4, entry 6). Either doubling the number of equivalents (entry 7), heating the reaction mixture (entry 8), or both (entry 10) reduced the reaction time but did not increase the isolated yield. The optimal conditions in THF consisted of heating the reaction mixture to 40 °C and using 2 equivalents of all reagents, which gave a 65% yield of **146**, based on aldimine **104**, after 16 h (entry 9). Additives such as TMS-Cl,[194] MeOH or an amino alcohol, each of which accelerate Et_2Zn addition to aldimines, did not improve the isolated yield or rate of reaction in CH_2Cl_2 or THF (entries 11-13).

The results in CH_2Cl_2 and THF were not promising, so toluene was investigated as the reaction solvent. When the entire one-pot reaction, including hydrozirconation at 40 °C for 1 h, was performed in toluene, 59% of **146** was isolated (Table 4, entry 14). However, when hydrozirconation was first performed in CH_2Cl_2 and then the solvent switched to toluene, gratifyingly

a 76% yield of **146** was isolated after 2 h (entry 15). When Me_2Zn was omitted from the reaction mixture, again no addition product was observed (entry 16); however, a catalytic amount of Me_2Zn resulted in nearly as high a yield as when using 1.5 equivalents of Me_2Zn, though the reaction time was significantly increased (entry 17). Again, additives such as MeOH or BnOH had no affect on the reaction yield (entries 18 and 19).

Table 4. Imine addition optimization studies.



Entry	Equiv **6**	Equiv Me_2Zn	Solvent	Temperature	Time (h)	Yield (%)[a]
1	1.5	1.5	CH_2Cl_2	rt	16	41
2	1.5	1.5	CH_2Cl_2	reflux	16	59
3	2.0	2.0	CH_2Cl_2	reflux	16	43
4	3.0	3.0	CH_2Cl_2	reflux	16	11
5	1.5	0	CH_2Cl_2	rt	4	0
6	1.5	1.5	THF	rt	36	54
7	3.0	3.0	THF	rt	16	50
8	1.5	1.5	THF	30 °C	20	49
9	2.0	2.0	THF	40 °C	16	65
10	3.0	3.0	THF	40 °C	4	52
11	1.5	1.5	CH_2Cl_2	rt	16	40[b]
12	1.5	1.5	CH_2Cl_2	reflux	16	64[c]
13	1.5	1.5	THF	rt	36	45[d]
14	1.5	1.5	toluene	rt	4	59
15	1.5	1.5	toluene[e]	rt	2	76
16	1.5	0	toluene[e]	rt	16	0
17	1.5	0.2	toluene[e]	rt	16	72
18	1.5	1.5	toluene[e]	rt	6	74[c]
19	1.5	1.5	toluene[e]	rt	6	74[f]

[a]Yields of isolated products are based on aldimine **104**. [b]0.1 equiv of $HO(CH_2)_2NMe_2$ was added. [c]0.5 equiv of MeOH was added. [d]1 equiv of TMS-Cl was added. [e]Hydrozirconation was performed in CH_2Cl_2, which was subsequently removed *in vacuo* and replaced with toluene. [f]0.5 equiv of $PhCH_2OH$ was added.

Using the optimized reaction conditions (Table 4, entry 15), the reaction scope was investigated (Table 5). Trisubstituted alkene **147** was prepared in high yield from 3-hexyne (entry 2). Functional groups on the alkyne such as silyl ethers (entry 3), silyl esters (entry 4), sulfonamides and carbamates (entry 5) were tolerated. Bulky trimethylsilylacetylene did not yield any significant quantities of the desired allylic amide **155** (entry 6). In contrast to Et_2Zn addition to **104**, electron-withdrawing groups on the benzaldimine did not affect the reaction (entry 7), whereas the presence of electron-donating groups significantly reduced the isolated yield (entry 8).

Other *N*-diphenylphosphinoylimines derived from non-enolizable aldehydes were prepared and subjected to these reaction conditions. Thus α,β-unsaturated aldimines **160** and **162** were converted to bis-allylic amides **161** and **163**, and alkynlimine **164** was converted to propargylamide **165** in 85% yield (Table 5, entries 9-11). The *N*-tosyl group was also suitable for activating benzaldimine **90** under these conditions (entry 12), and *N*-tosylimines **166**, **168** and **170**, derived from enolizable aldehydes, formed amides **167**, **169** and **171** (entries 13-15).

Table 5. Synthesis of allylic amines using the Zr-Zn transmetalation methodology.

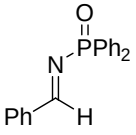
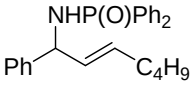
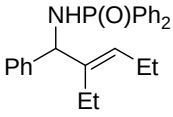
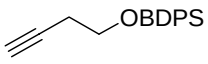
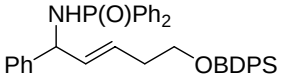
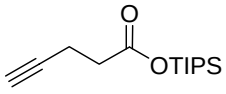
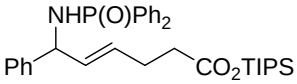
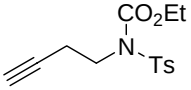
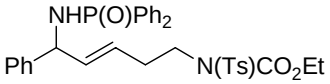
Entry	Alkyne	Aldimine	Allylic Amine	Yield (%)
1	1-hexyne (**30**)	 **104**	 **146**	76
2	3-hexyne	**104**	 **147**	72
3	 **148**	**104**	 **149**	73
4	 **150**	**104**	 **151**	65
5	 **152**	**104**	 **153**	59

Table 5 (continued). Synthesis of allylic amines using the Zr-Zn transmetalation methodology.

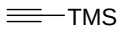
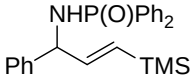
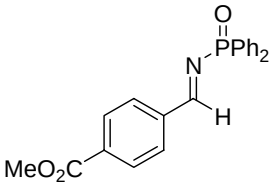
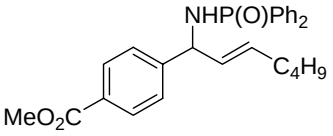
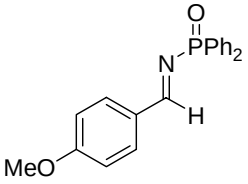
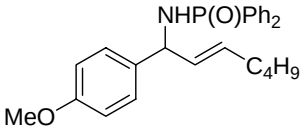
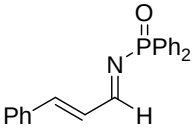
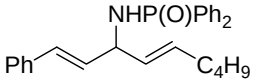
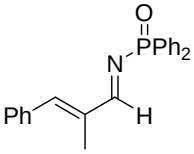
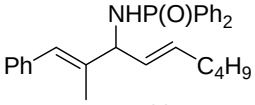
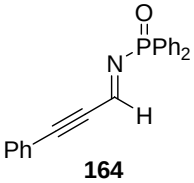
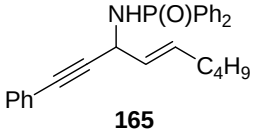
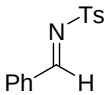
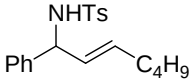
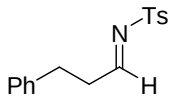
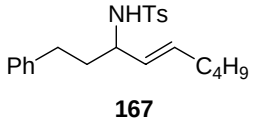
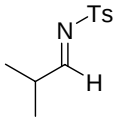
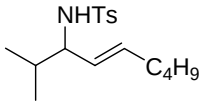
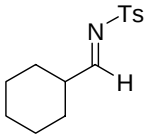
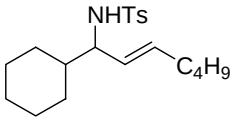
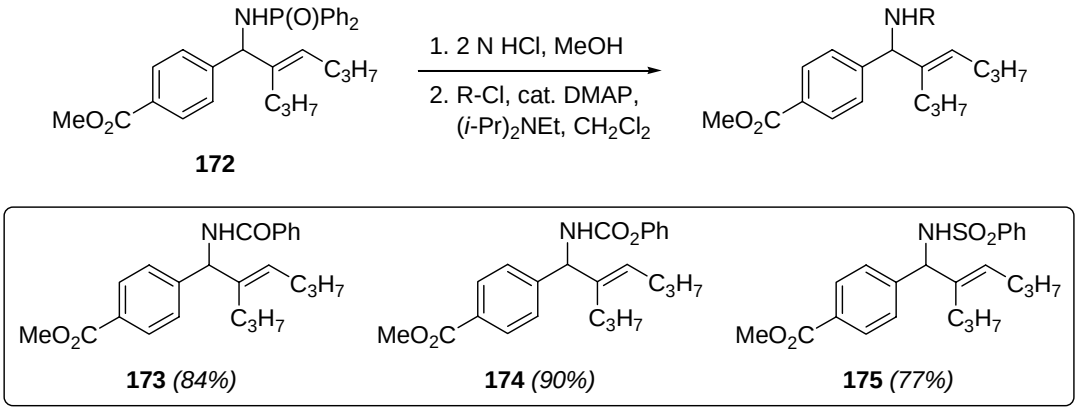
Entry	Alkyne	Aldimine	Allylic Amine	Yield (%)
6	 **154**	**104**	 **155**	< 10
7	**30**	 **156**	 **157**	84
8	**30**	 **158**	 **159**	35
9	**30**	 **160**	 **161**	28
10	**30**	 **162**	 **163**	72
11	**30**	 **164**	 **165**	85
12	**30**	 **90**	 **91**	80
13	**30**	 **166**	 **167**	90
14	**30**	 **168**	 **169**	71

Table 5 (continued). Synthesis of allylic amines using the Zr-Zn transmetalation methodology.

Entry	Alkyne	Aldimine	Allylic Amine	Yield (%)
15	**30**	 **170**	 **171**	81

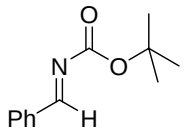
[a]Reaction conditions: (i) 1.5 equiv of Cp_2ZrHCl, 1.5 equiv of alkyne, CH_2Cl_2, rt, 10 min; (ii) 1.5 equiv of Me_2Zn, toluene, -78 °C, 5 min; (iii) 1.0 equiv of aldimine, toluene, rt, 2-5 h. [b]Yields of isolated products are based on aldimines.

Like benzyl phosphinamide **106**, the allylic phosphinamides prepared were easily deprotected under mild conditions.[195] For example, anhydrous HCl in MeOH removed the diphenylphosphinoyl group of **172**, and in one pot the allylic amine was reprotected as amide **173**, carbamate **174** or sulfonamide **175** (Scheme 33).

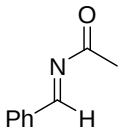


Scheme 33. Facile one-pot deprotection and derivitization of allylic phosphinamide **172**.

Several other aldimines were tested using the conditions of Table 5. Carbamoylimines such as **175**, and *N*-acetylimine **177** were significantly more reactive than phosphinimine **104** or sulfonimine **90** (*vide infra*). All benzaldimines that did not have an activating (strongly withdrawing) group on nitrogen, including *N*-aryl imine **178**, *N*-silyl imine **179**, and oxime **180**, were unreactive under the Zr-Zn transmetalation conditions.



176



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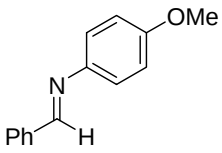

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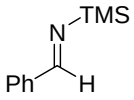

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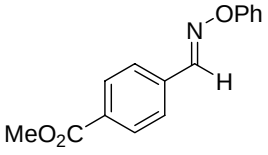
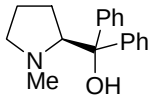


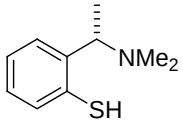
180

2.2. Asymmetric Synthesis of Allylic Amines

Development of an asymmetric synthesis of **144**, through the use of chiral amino alcohol or thiol promoters that were effective for the enantioselective allylic alcohol reaction detailed in Scheme 13, was unsuccessful. Amino alcohol **55** and amino thiophenol **181** were used for the



55

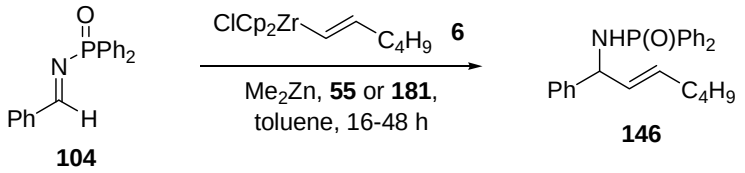


181

attempted *ee* optimization studies (Table 6). Both were effective asymmetric catalysts for the Zr-Zn transmetalation/aldehyde addition reaction, and both can easily be prepared in large scale in two steps from inexpensive, commercially available starting materials.

Optimization was performed for the addition of alkenylzirconocene **6** to imine **104**. Using the standard conditions of toluene as the reaction solvent and performing the reaction at room temperature gave acceptable yields of **146** but less than 5% *ee* when 10 or 50 mol% of **55** was added to the reaction mixture (Table 6, entries 1 and 2). The same occured when amino thiol **181** was used with a reaction temperature of 0 °C (entries 3 and 4). For phosphinimine **104**, when the reaction was performed at -20 °C there was a significant drop in the rate of reaction, and only a very small *ee* was measured by chiral HPLC (entry 5).

Table 6. Attempted asymmetric addition reactions with imine **104** and ligands **55** and **181**.



104 **146**

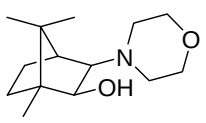
Entry	Equiv Me_2Zn	L*	Equiv L*	Temperature	Yield (%)[a]	*ee* (%)[b]
1	1.2	**55**	0.1	rt	65	< 5
2	1.2	**55**	0.5	rt	71	< 5
3	1.5	**181**	0.1	0 °C	68	< 5
4	1.5	**181**	0.5	0 °C	69	< 5
5	1.5	**181**	0.1	-20 °C	39	10
6	1.0	**55**	1.0	rt	0	-
7	3.0	**55**	1.0	rt	66	24
8	3.0	**55**	1.0	10 °C	75	23
9	3.0	**55**	1.0	0 °C	27	29
10	3.0	**181**	1.0	10 °C	56	34
11	0.2	**181**	0.5	50 °C	56	18

[a]Yields of isolated products based on **104**. [b]Measured by chiral HPLC using a Chiracel OD or AD Column.

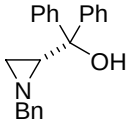
Though the reaction was largely unaffected by the presence of substoichiometric quantities of ligand when at least one equivalent of Me_2Zn was used, addition of one equivalent of **55** to an equal amount of Me_2Zn suppressed addition of alkenylzirconocene **6** to imine **104** (Table 6, entry 6). The use of stoichiometric quantities of **55** required 3 equivalents of Me_2Zn for an acceptable isolated yield of **146**, but the *ee* of the reaction was still not high (entry 7). Lowering the temperature did not significantly increase the *ee*, and once again reduced the rate of reaction (entries 8 and 9). The highest *ee* of allylic phosphinamide **146** (34%) was achieved using three equivalents of Me_2Zn, one equivalent of **181**, and performing the reaction in toluene at 10 °C (entry 10). The reaction could be forced to completion when equal or greater amounts of amino alcohol than Me_2Zn were used, by heating to 50 °C. However, when 0.2 equivalents of Me_2Zn and 0.5 equivalents of **181** were used at 50 °C, the reaction *ee* was only 18% (entry 11). The observed *ee*'s, though low, were reproducible. Repeating reactions using one equivalent of ligand that gave *ee's* in the range of 20-30% gave a result that was within 5% *ee* of the originally measured value. In every set of reaction conditions tested for an asymmetric synthesis of **146**,

where less than one equivalent of ligand but at least one equivalent of Me_2Zn was used, the *ee* was always <10%.

Several other ligands were prepared and tested using the conditions of Table 6, entries 8 and 10. These included amino alcohols **108**,[b] **112**,[b] **127**,[196] **182**, **183**,[197] **184**,[198] **185**,[199] **186**,[200] **187**, and **188**, alcohols **189** and **190**, and amines **191**-**193**. In all cases, the *ee* was <30%. Pyridine **189** was prepared as a racemic mixture and then separated by semi-preparative chiral



182 [(-)-MIB]



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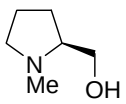

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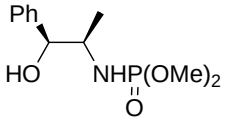

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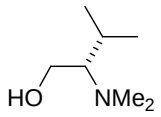

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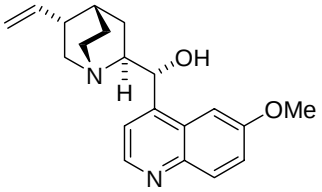
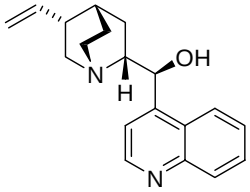
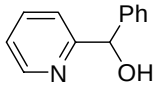


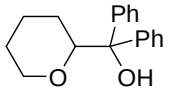
187 (quinine)



188 (cinchonine)



189



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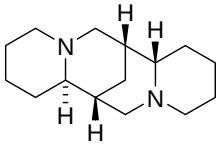
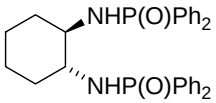
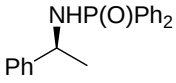


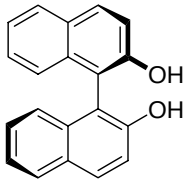
191 [(-)-sparteine]



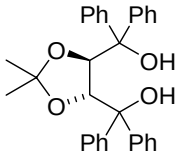
192



193



194 [(+)-BINOL]

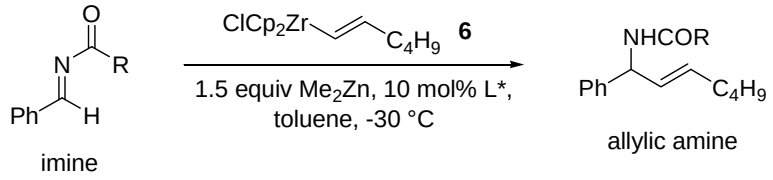


195

HPLC using a Chiralcel AD column. The enantiomerically pure ligand (*S*)-**189** was effective for Et_2Zn addition to phosphinimine **104** using the conditions of Table 1 (α-ethylbenzylamine (*S*)-**106** was isolated in 74% yield with an *ee* of 93%), but was ineffective for the preparation of enantiomerically enriched allylic phosphinamide **146**. Based on the results of Scheme 14, alcohol **190** was also prepared as a racemic mixture and separated by chiral HPLC, but was also inneffective. Diols **70**,[201] **194** and **195**[202] were also tested, in combination with Ti(IV) reagents. Regardless of the conditions used, when Ti was present in the reaction mixture, the *ee* was zero. *N*-Tosylimine **90** was also completely ineffective, with only racemic product formed. Using $ZnCl_2$ in place of Me_2Zn was also briefly investigated, however the *ee*'s were zero in all reactions tested.

N-Carbamate, -amide, and -urea benzaldimines **176**, **177**, **197**, **199**, and **202** were significantly more reactive than phosphinimine **96**, thus temperatures lower than those of Table 6 could be investigated (Table 7). Again, no *ee* higher than 35% was obtained. The allylic amine derivatives were however typically isolated in higher yield.

Table 7. Attempted asymmetric addition reactions with more reactive imines.



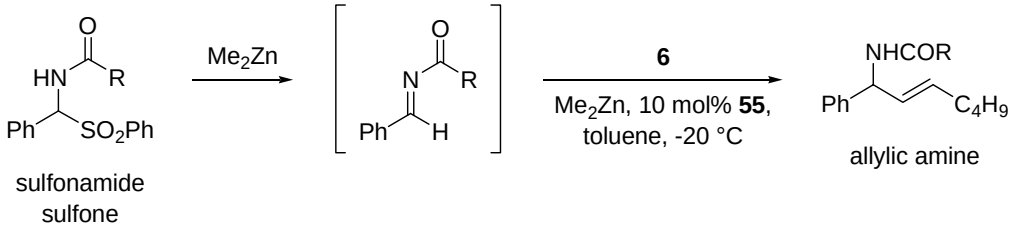
Entry	R	Imine	L*	Yield (%)[a]	*ee* (%)[b]	Allylic Amine
1[c]	O*t*-Bu	**176**	**55**	81	22	**196**
2	OEt	**197**	**181**	94	7	**198**
3[d]	OMe	**199**	**55**	86	6	**200**
4	Me	**177**	**181**	44	1	**201**
5	NMe_2	**202**	**181**	69	6	**203**

[a]Yields of isolated products, based on imines. [b]Measured by chiral HPLC using a Chiracel OD or AD Column. [c]1 equiv of Me_2Zn used. [d]3 equiv of Me_2Zn and 1 equiv of L* used, and reacted at -20 °C.

The benzaldimines **176**, **177**, **197**, and **199** could be prepared *in situ* using the method of Dahmen and Bräse (Table 8). The advantage of this method was the ease of preparation and the stability of the solid sulfonamide sulfones, compared to the aldimines which were all moisture-sensitive oils. However, as can be seen by comparing Table 7, entry 2 and Table 8, entry 1, the isolated yield of ethyl carbamate **198** was much lower using the *in situ* generated imine protocol. The isolated yield of acetamide **201** was very slightly increased (Table 7, entry 4 vs. Table 8, entry 2), likely due to the difficulty in handling the very unstable imine **177**. This approach was abandoned because no *ee* above 10% was obtained using *in situ* generated imines.

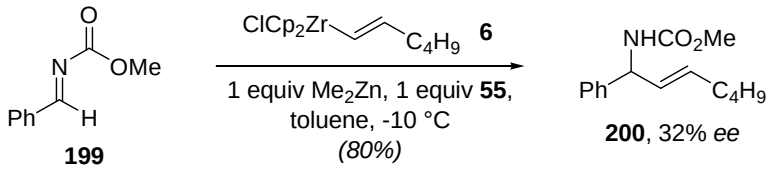
The highest *ee* achieved using an imine other than **104** was from addition to **199**, in the presence of 1 equivalent of both Me_2Zn and amino alcohol **55**, which yielded 80% of allylic carbamate **200** in 32% *ee* (Scheme 34).

Table 8. Attempted asymmetric addition reactions with *in situ*-generated imines.



Entry	R	Sulfonamide Sulfone	Yield (%)[a]	*ee* (%)[b]	Allylic Amine
1	OEt	**204**	51	5	**198**
2	Me	**205**	48	6	**201**

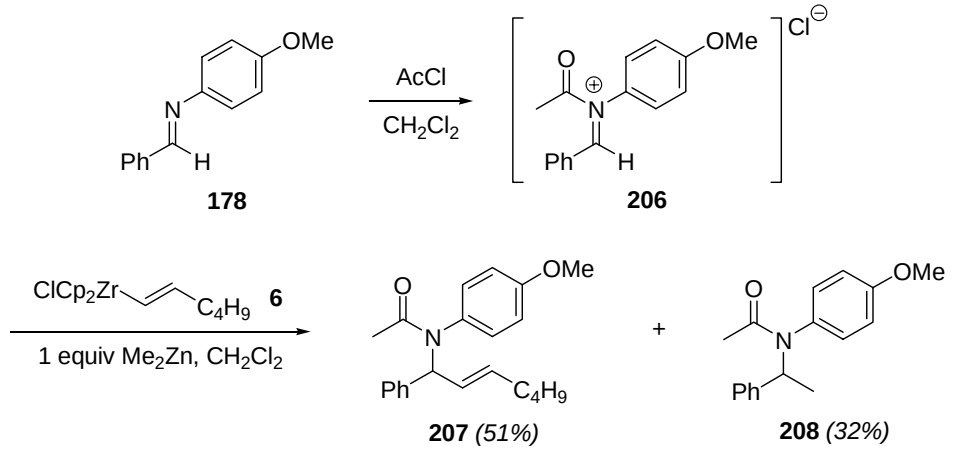
[a] Yields of isolated products, based on sulfones. [b] Measured by chiral HPLC using a Chiracel OD or AD Column.



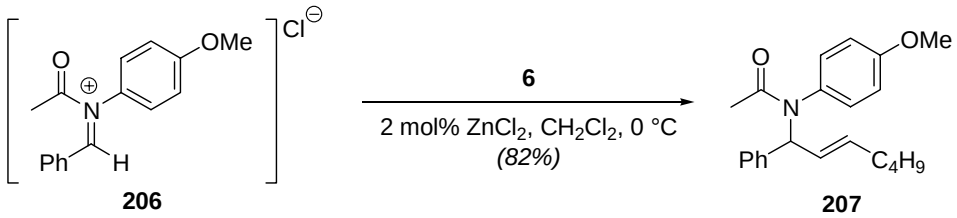
Scheme 34. Highest *ee* achieved for addition to an imine other than **104**.

Following a recently published protocol,[203] *in situ* generated acyliminium ions were used as electrophiles in the Zr-Zn transmetalation reaction, and found to be significantly more reactive than any other imines tested. Quantitative formation of acyliminium chloride **206** took 15 min at room temperature in CH_2Cl_2 and could be monitored by TLC. Treatment of **206** with hexenyl-zirconocene **6** and an equivalent of Me_2Zn resulted in very rapid 1,2-addition, though a significant amount of methyl addition also occurred. When the reaction was performed at room temperature, 51% of the desired allylic amide **207** was isolated, as well as 32% of methyl-adduct **208** (Scheme 35).

To avoid methyl transfer to acyliminium **206**, $ZnCl_2$ was successfully used in place of Me_2Zn (Scheme 36). During optimization of these reaction conditions, it was discovered that as little as 1 drop of a 1.0 M solution of $ZnCl_2$ in Et_2O was sufficient to catalyze the addition of hexenylzirconocene **6**; after only a 15 min reaction time at 0 °C, 82% of **207** was isolated. There was no addition when $ZnCl_2$ was excluded from the reaction.



Scheme 35. Hexenylzirconocene **6** addition to acyliminium chloride **206** in the presence of stoichiometric Me_2Zn.

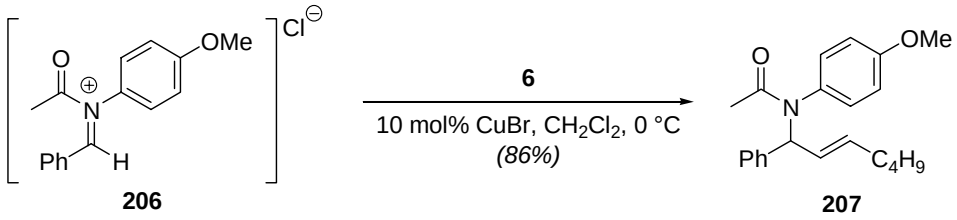


Scheme 36. Hexenylzirconocene **6** addition to acyliminium chloride **206** in the presence of catalytic $ZnCl_2$.

Despite the presence of a significantly more reactive electrophile and the high yield of addition product **207** with only 2 mol% of $ZnCl_2$ added, no *ee* was obtained when the reaction was performed in the presence of chiral amino alcohols or thiols. As previously, using an equal amount of ligand and $ZnCl_2$ had a detrimental affect on the rate of reaction, whereas if more $ZnCl_2$ than ligand was used only racemic product was formed. Unlike all of the other imines tested; however, the addition of **6** to **206** was also catalyzed by Cu(I) salts (Scheme 37). In the presence of 10 mol% of CuBr, allylic amide **207** was isolated in 86% yield after a 30 min reaction time at 0 °C.

All Cu(I) salts tested were almost equally effective, so CuCl was selected for asymmetric studies since Cp_2ZrCl_2 (the Zr complex formed after transmetalation in this case) is not highly soluble in CH_2Cl_2. Several known asymmetric ligands for Cu-catalyzed reaction were tested, including **209**-**217** (Figure 4) No ligand was found that delivered any enantioselectivity (<10%

ee for each catalyst system tested), and again the rate of reaction was decreased upon addition of an external ligand to the reaction mixture.



Scheme 37. Hexenylzirconocene **6** addition to acyliminium chloride **206** in the presence of catalytic CuBr.

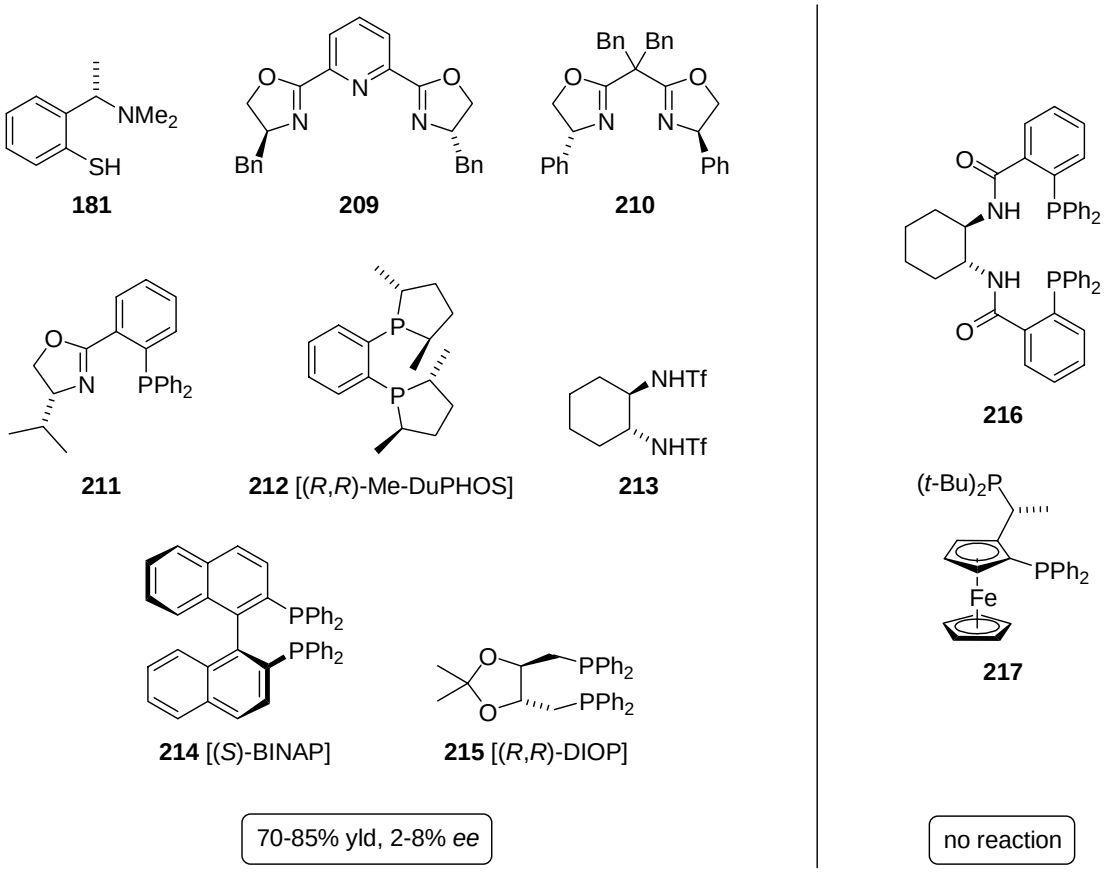
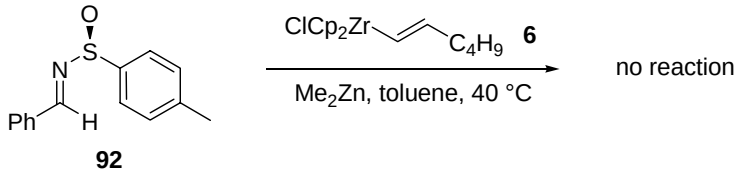


Figure 4. Ligands tested and *ee's* obtained for the attempted Cu-catalyzed asymmetric synthesis of **207**.

Lacking success using external chiral ligands for an asymmetric synthesis of allylic amines using the Zr-Zr transmetalation methodology, other strategies were explored. Diastereo-

selective addition to chiral sulfinimine **92** was attempted; however, this aldimine was not sufficiently reactive, even at elevated temperatures (Scheme 38).

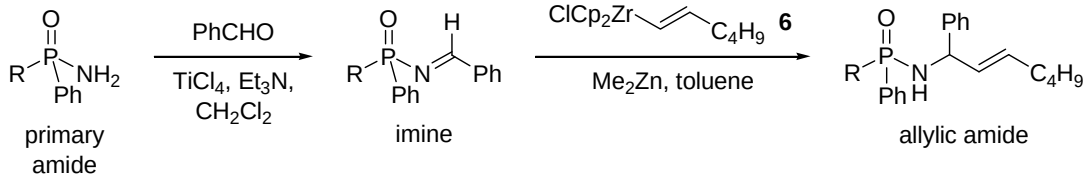


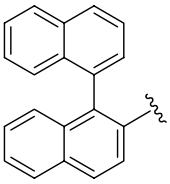
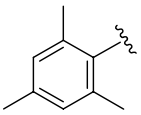
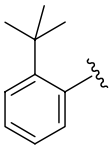
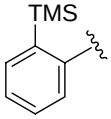
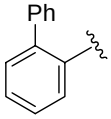
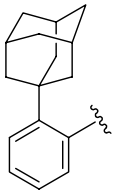
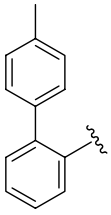
Scheme 38. Attempted diastereoselective addition to a chiral sulfinimine.

Several chiral phosphinamides were prepared and tested as potential substrates for diastereoselective addition of alkenylzirconocene **6** (Table 9). The first imine tested was binaphthyl-phenyl phosphinimine **219**, which was prepared as a single diastereomer (*vide infra*). Addition of **6** to this imine at room temperature afforded the desired allylic amide **220** with a modest diastereomeric ratio of 72:28 (entry 1). The benzaldimines of known phosphinamides **221**[204] and **224**[205] were then tested and identical diastereoseletivities of 69:31 were obtained for both (entries 2 and 3). Since there was no change in selectivity for all three substrates tested, it was assued that the bulky R group was not as hoped involved in stereodifferentiation, instead the constant *dr* of 7:3 was due to the difference in size between the phenyl and oxygen substituents on phosphorous.

Preliminary molecular modeling showed that *ortho*-substituted phenyl rings blocked one face of the aldimine and oriented the oxygen away from the C=N double bond. A series of novel phosphinamides were prepared to test the modeling findings. Though the first two imines tested, **227** and **230**, had poorer selectivities of nearly 1:1 (Table 9, entries 4-6), the reaction was much slower, and imine **227** required 40 °C for an isolated yield of 68%. In these cases, due to the lower rate of reaction, it appeared that the transition state was more crowded thus the model appeared to be correct. Imines **233** and **236** were then tested (entries 7 and 8). In both cases a reaction temperature of 40 °C was required, and the diastereoselectivity was increased, though it was still much too low to be useful. Imine **239** showed no improvement over **233** (entry 9).

Table 9. Diastereoselective addition to chiral phosphinimines.

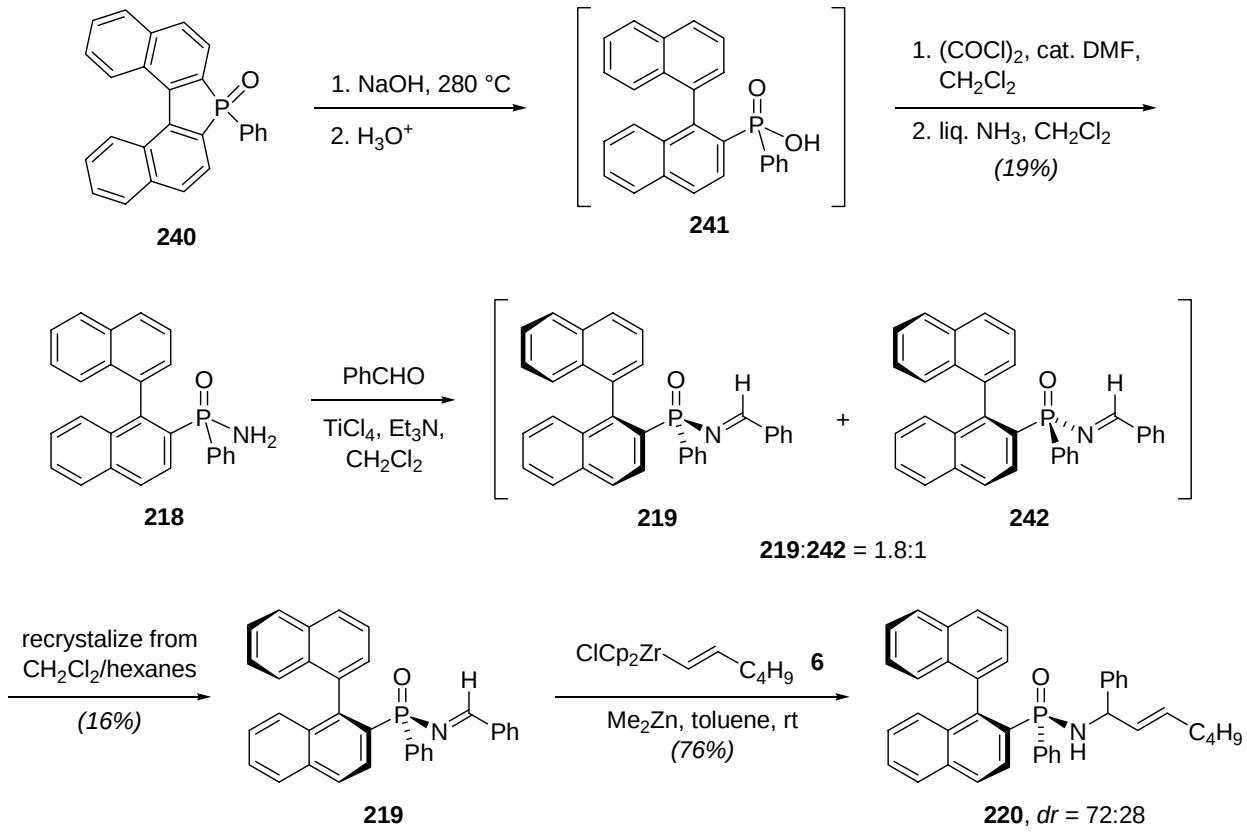


Entry	Primary Amide	R	Imine	Yield[a]	Allylic Amide	Temperature	Yield[b]	*dr*
1	**218**		**219**	16%	**220**	rt	76%	72:28
2	**221**		**222**	35%	**223**	rt	53%	69:31
3	**224**	*t*-Bu	not isolated	--	**225**	rt	32%	69:31
4	**226**		not isolated	--	**227**	rt	51%	57:43
5	**226**		not isolated	--	**227**	40 °C	68%	54:46
6	**228**		**229**	87%	**230**	rt	70%	51:49
7	**231**		**232**	82%	**233**	40 °C	89%	65:35
8	**234**		**235**	97%	**236**	40 °C	86%	59:41
9	**237**		**238**	88%	**239**	45 °C	87%	63:37

[a]Isolated yields of Imines. [b]Isolated yields of Allylic Amides.

The imines were prepared using the method of Jennings and Lovely,[206] and initially isolated, with difficulty, by precipitation. Imines **225** and **227** could not be isolated by this method, and so they were used as crude mixtures of imine and benzaldehyde. Imines **230**, **233**, **236**, and **239** were purified by column chromatography after it was discovered that unlike diphenylphosphinamide **104**, these imines were stable on deactivated SiO_2.

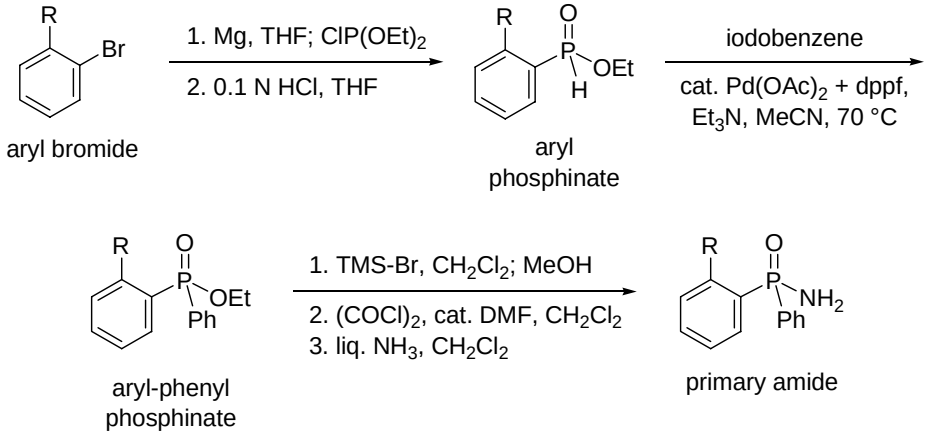
Binaphthyl-phenyl phosphinimine **219** was prepared from the known phosphinic acid **241**[207] in three steps (Scheme 39). Thermal opening of phosphole oxide **240** with NaOH was very low yielding. The subsequent one-pot acid chloride formation and amidation was nearly quantitative. Imine formation afforded a 64:38 mixture of diastereomers, and fortunately, crystalization from CH_2Cl_2/hexanes afforded an x-ray quality (Appendix A) single crystal that was characterized and tested in the diastereoselective addition.



Scheme 39. Synthesis and of binaphthyl-phenyl phosphinimine **219**.

The novel phosphinamides **243**, **246**, **248**, **250**, and **252** were prepared by adapting the literature procedure used for mesityl-phenyl phosphinamide **221** (Table 10). Aryl Grignard addition to $ClP(OEt)_2$ was followed by mild acid-promoted rearrangement to afford ethyl phosphinates with a characteristic P-H coupling of ~550 Hz. Only **244** (R = *t*-Bu) was isolated (entry 1), in all other cases the crude material was used in the subsequent Pd-catalyzed coupling with iodobenzene. Phosphinates **245**, **247**, **249**, **251**, and **253** were isolated in modest to high yield. For entries 2-5, a three-step, high yielding sequene of dealkylation, acid chloride formation, and amidation was used for ester to amide conversion. Non-racemic phosphinamide **221** has been prepared by treating its corresponding acid chloride with one enantiomer of α-methylbenzylamine, separating the resulting diastereomers by chromatography on SiO_2, and removal of the benzylic group by hydrogenation. This resolution strategy was not explored here since no highly diastereoselective alkenylzirconocene addition was found.

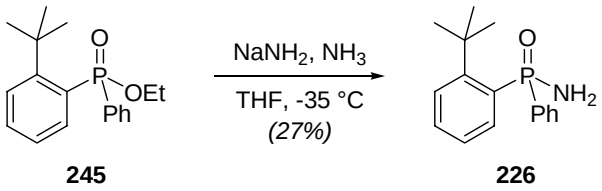
Table 10. Synthesis of novel aryl-phenyl phosphinamides.



Entry	Aryl Bromide	R	Aryl Phosphinate	Yield[a]	Aryl-Phenyl Phosphinate	Yield[b]	Primary Amide	Yield[c]
1	**243**	*t*-Bu	**244**	95%	**245**	60%	**226**	---
2	**246**	TMS	not isolated	--	**247**	28%	**228**	88%
3	**248**	Ph	not isolated	--	**249**	82%	**231**	95%
4	**250**	1-adamantyl	not isolated	--	**251**	48%	**234**	61%
5	**252**	*p*-tolyl	not isolated	--	**253**	54%	**237**	87%

[a]Isolated yield of Aryl Phosphinates. [b]Isolated yield of Aryl-Phenyl Phosphinates. [c]Isolated yield of Primary Amides.

For the conversion of ester **245** to amide **226**, a known one-step protocol using $NaNH_2$ was followed, but the yield was low and the reaction was not clean (Scheme 40). This appraoch failed completely for the conversion of **247** to **228**, so the three-step sequence shown in Table 10 was used for all other substrates.

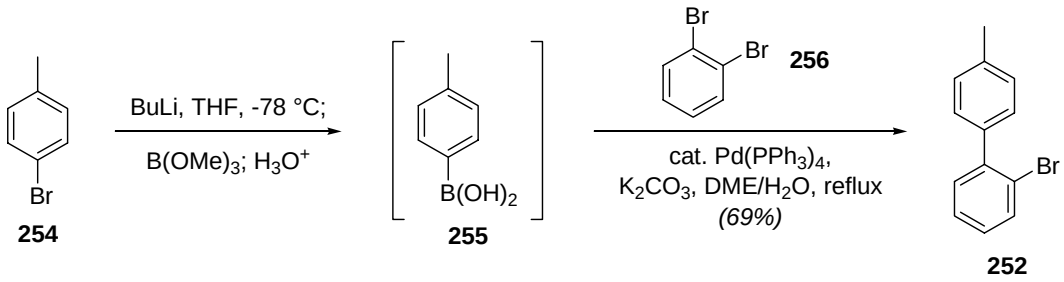


245 **226**

Scheme 40. One-step synthesis of phosphinamide **226**.

Known aryl bromides **243**,[208] **246**,[209] and **250**[210] were prepared according to literature procedures. Tolyl-substituted bromobenzene **252** was prepared by Suzuki coupling of 4-methyl-phenylboronic acid (**255**) with 1,2-dibromobenzene (Scheme 41).

This diastereolective addition strategy was abandonded since the diastereoselectivities obtained were not promising, and preparation of the chiral phosphinimines required up to eight chemical steps, not including the needed resolution should the method be used for the synthesis of non-racemic allylic amines.



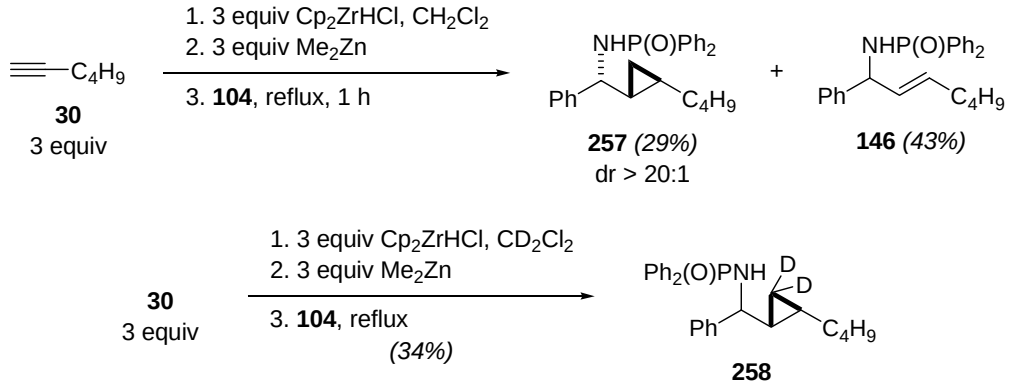
254 **255** **252**

Scheme 41. Synthesis of aryl bromide **252**.

2.3. Synthesis of *C*-Cyclopropylalkylamines

While investigating the alkenylzinc addition to aldimines in CH_2Cl_2 (Table 4), it was observed that increasing the number of equivalents of the organometallic reagents when

performing the reaction at reflux reduced the isolated yield of the desired allylic amide **146**. This was due to formation of a second phosphinamide, cyclopropane **257** (Scheme 42). Only the amino cyclopropane with *anti*-configuration (determined by X-ray analysis of benzyl derivative **268**, Appendix B) was identified by ^{1}H NMR analysis of the crude reaction mixture. By repeating the reaction in CD_2Cl_2, bis-deuterated cyclopropane **258** was formed, whereas **257** remained the major product formed if Me_2Zn was replaced with Et_2Zn, thus the origin of the new cyclopropyl carbon was shown to be the solvent.



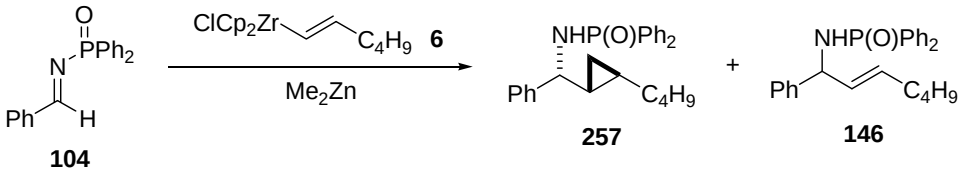
Scheme 42. Unexpected formation of amino cyclopropane **257**.

Allowing the reaction to continue for a longer period of time increased the yield of **257** and decreased that of **146** (Table 11, Entry 2). Lowering the number of equivalents of the organometallic reagents reduced the yield of **257**, even after prolonged reaction times (Entries 3 and 4). Even as little as 10 equivalents of CH_2Cl_2 added to a reaction performed in toluene resulted in formation of substantial quantities of **257**, though heating was necessary to keep the reaction time under 24 h (Entries 5 and 6). Whenever CH_2Cl_2 was used, **257** was not the only product formed, thus, in order to increase the yield and rate of the reaction, CH_2I_2 was added to the reaction mixture, resulting in the isolation of **257** in 74% yield (Entry 7).

The scope of the optimized reaction conditions (Table 11, entry 7) is shown in Table 12. Silyl ether, silyl ester, sulfonamide, and carbamate functional groups were again tolerated on the alkyne moiety (entries 2-4).[211] Alkynylimine **164** was converted into propargylamine **262**[212] in modest yield (entry 5); however, the α,β-unsaturated imines **159** and **161** gave only complex mixtures of mono- and bis-cyclopropanated amides. Use of *N*-tosylimine **90** in place of **104**

retained the excellent diastereoselectivity displayed by all reactions thus far (entry 6); however, with alkylimines **166** and **170**, the diastereoselectivity was lower (entries 7 and 8).

Table 11. *C*-Cyclopropylalkylamine reaction optimization.



104 **257** **146**

Entry	Equiv **6** and Me_2Zn	Solvent	Temperature	Time (h)	Yield **257**[a]	Yield **146**[a]
1	3.0	CH_2Cl_2	reflux	1	29%	43%
2	3.0	CH_2Cl_2	reflux	16	58%	11%
3	2.0	CH_2Cl_2	reflux	16	18%	43%
4	1.2	CH_2Cl_2	reflux	16	4%	42%
5	3.0	toluene[b]	rt	36	43%	26%
6	3.0	toluene[b]	40 °C	16	49%	19%
7	3.0	CH_2Cl_2[c]	reflux	3	74%	---

[a]Yields of isolated products based on **104**. [b]10 equiv CH_2Cl_2 added to reaction mixture. [c]5 equiv CH_2I_2 added to the reaction mixture after 1 h.

Table 12. Synthesis of *C*-cyclopropylalkylamines.

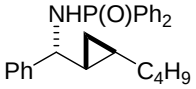
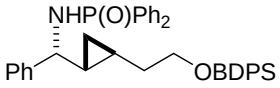
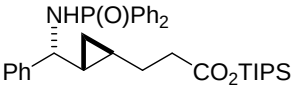
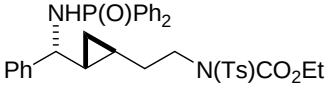
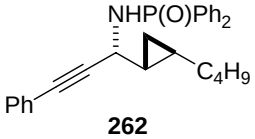
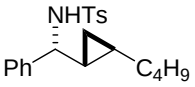
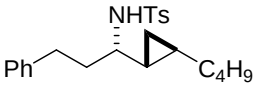
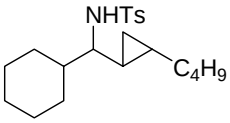
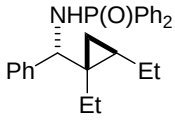
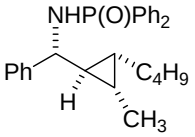
Entry	Alkyne	Aldimine	*C*-Cyclopropylalkylamine[a,b]	Yield[c]	*dr*
1	1-hexyne (**30**)	**104**	 **257**	74%	97:3[d]
2	**148**	**104**	 **259**	68%	98:2[d]
3	**150**	**104**	 **260**	71%	>95:5[e]
4	**152**	**104**	 **261**	45%	>95:5[e]

Table 12 (continued). Synthesis of *C*-cyclopropylalkylamines.

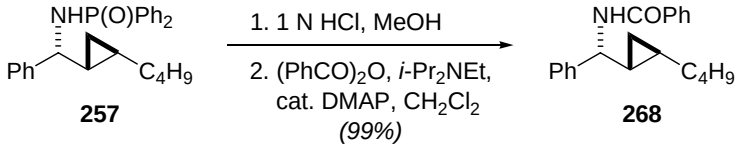
Entry	Alkyne	Aldimine	*C*-Cyclopropylalkylamine[a,b]	Yield[c]	*dr*
5	**30**	**164**	 **262**	60%	>95:5[e]
6	**30**	**90**	 **263**	66%	>95:5[e]
7	**30**	**166**	 **264**	67%	87:13[e]
8[f]	**30**	**170**	 **265**	62%	40:60[e,g]
9	3-hexyne	**104**	 **266**	46%	96:4[d]
10[h,i]	**30**	**104**	 **267**	52%	>95:5[e,j]
11[k]	**30**	**104**	**257**	91%	>95:5[e]

[a]Only the major isomer is shown. [b]Reaction conditions: (i) 3 equiv of Cp_2ZrHCl, 3 equiv of alkyne, CH_2Cl_2, rt, 10 min; (ii) 3 equiv of Me_2Zn, CH_2Cl_2, -78 °C, 5 min; (iii) 1 equiv of aldimine, CH_2Cl_2, reflux, 1-2 h; (iv) 5 equiv of CH_2I_2, CH_2Cl_2, reflux, 2-12 h. [c]Yields of isolated products are based on aldimines. [d]Determined by HPLC analysis of the crude reaction mixture. [e]Determined by ^1H NMR analysis of the crude reaction mixture. [f]Additional Me_2Zn (3 equiv) and CH_2I_2 (10 equiv) were added to the reaction mixture. [g]Major diastereomer was not assigned. [h]Et_2Zn (6 equiv) and CH_3CHI_2 (12 equiv) were added to the reaction mixture. [i]Hydrozirconation was performed in THF, and the solvent exchanged to $(CH_2Cl)_2$ for the remainder of the reaction. [j]Relative stereochemistry determined by x-ray analysis of a derivative (Appendix C). [k]1 equiv of $PhCH_2OH$ was added to the reaction mixture.

1,1,2-Trisubstituted cyclopropanes could be prepared in modest yield using internal alkynes in the hydrozirconation step (Table 12, entry 9), and 1,2,3-trisubstituted cyclopropanes

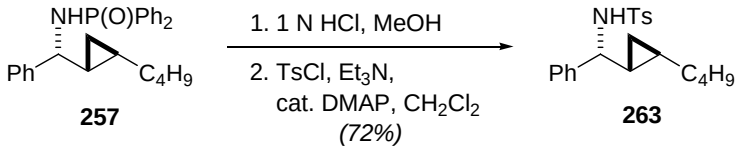
could also be prepared using CH_3CHI_2 in place of CH_2I_2 (entry 10). Using $I_2C(CH_3)_2$[213] afforded only trace amounts of the desired tetrasubstituted cyclopropane. When either of these 1,1-diiodoalkanes were used in place of CH_2I_2, hydrozirconation had to be performed in a solvent other than CH_2Cl_2, otherwise **257** was the major product formed. The isolated yield of **257** was increased to 91% when one equivalent of benzyl alcohol was added to the reaction mixture (entry 11).

The *C*-cyclopropylalkylphosphinamides produced could be easily deprotected in quantitative yield in anhydrous methanol and acid (Scheme 43). Upon acylation, benzamide **268** (used for X-ray analysis to determine the relative stereochemistry, Appendix B) was formed in 99% yield from **257**.



Scheme 43. Deprotection of phosphinamide **257**.

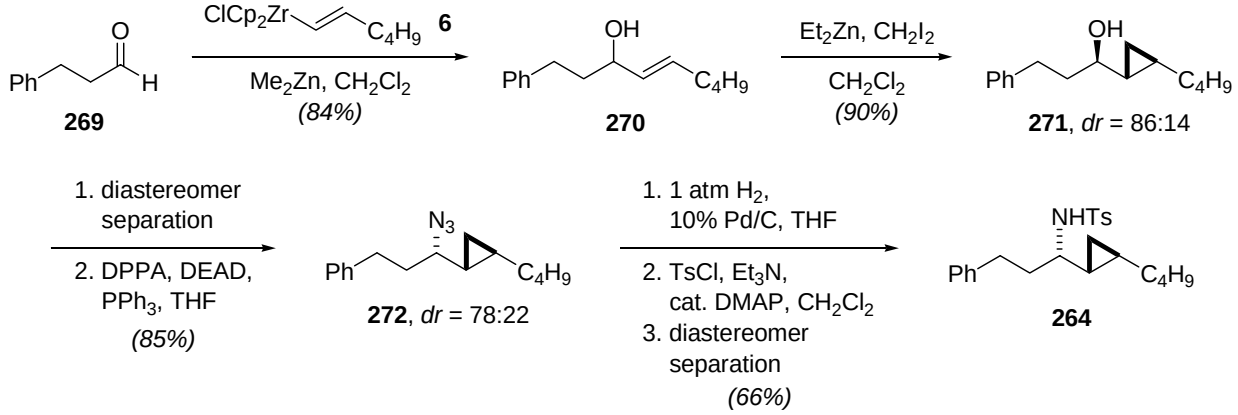
The *anti*-configuration was observed for the major diastereomer of all *C*-cyclopropyl-alkylamines but **265**. The stereochemistry of **259**-**261** and **266** were assigned by analogy to **257**. Deprotection and *N*-tosylation of **257** afforded **263**, confirming an identical relative configuration for the major diastereomers of *N*-phosphinoyl and *N*-sulfonyl amides (Scheme 44).



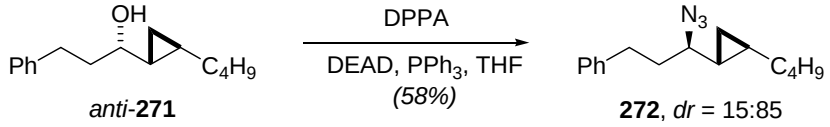
Scheme 44. Relative stereochemistry determination of **263** by chemical correlation to **257**.

The relative stereochemistry of **264** was determined by chemical correlation (Scheme 45). Known allylic alcohol **270** was prepared using the Zr-Zn transmetalation/aldehyde addition reaction. Simmons-Smith cyclopropanation of **270** with the Furukawa reagent afforded an 86:14 mixture of easily separable diastereomers, with the major isomer assigned a *syn*-relative

stereochemistry based on literature precedent. Mitsunobu substitution of the secondary alcohol of *syn*-**271** with DPPA[214] gave a 78:22 mixture of diastereomeric azides. The major epimer was assigned as the S_N2 product (*anti* relative stereochemistry), since subjecting the minor diastereomer from Simmons-Smith cyclopropanation (*anti*-**271**) to the Mitsunobu reaction afforded the azides as a 15:85 mixture of diastereomers, favoring the *syn*-stereoisomer (Scheme 46).[215] Reduction of the mixture of azides followed by *N*-tosylation and epimer separation by chromatography on SiO_2 afforded **264** in 66% overall yield.

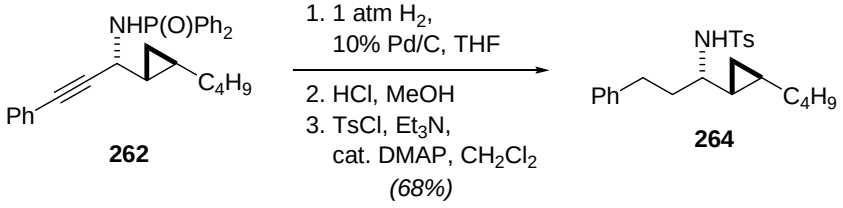


Scheme 45. Relative stereochemistry determination of **264** by an alternate synthesis.



Scheme 46. Mitsunobu reaction on *anti*-**271**.

The relative configuration of **262** was determined chemically by reduction, deprotection, and tosylation to give **264** (Scheme 47).



Scheme 47. Relative stereochemistry determination of **262** by chemical correlation to **264**.

A Simmons-Smith-type cyclopropanation was postulated to explain the formation of **257** (Figure 5). Hydrozirconation of 1-hexyne followed by transmetalation with Me_2Zn afforded alkenylzinc **31**. Addition to aldimine **104** resulted in metalated allylic amide **273**, which reacted with CH_2Cl_2 to give zinc carbenoid **274**. Intramolecular cyclopropanation of **274** gave *anti*-cyclopropane **257**. No reaction occurred in the absence of Me_2Zn. TLC analysis of the reaction mixture clearly showed formation of allylic amide **146** prior to formation of cyclopropane **257**, and there was no addition of a cyclopropylzinc species (prepared according to the conditions of Scheme 31) to imine **104**.

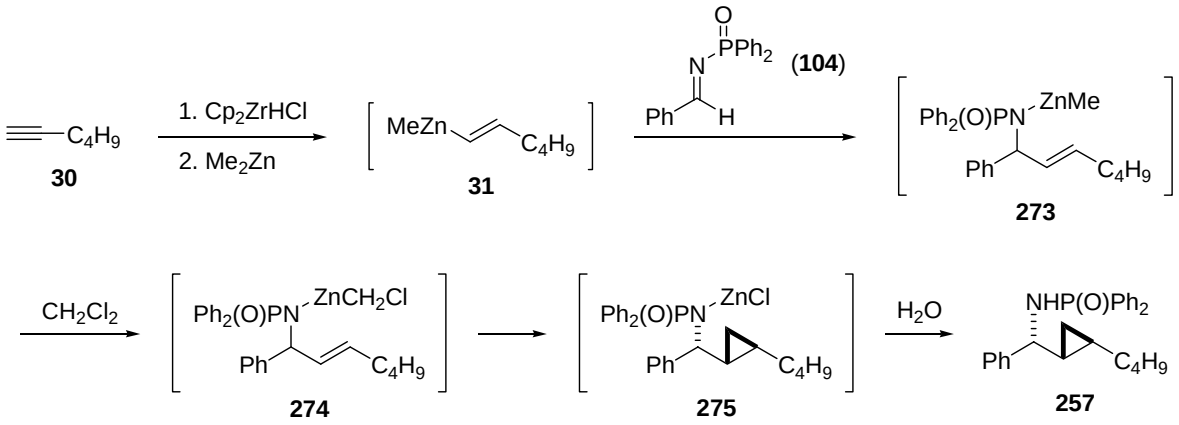
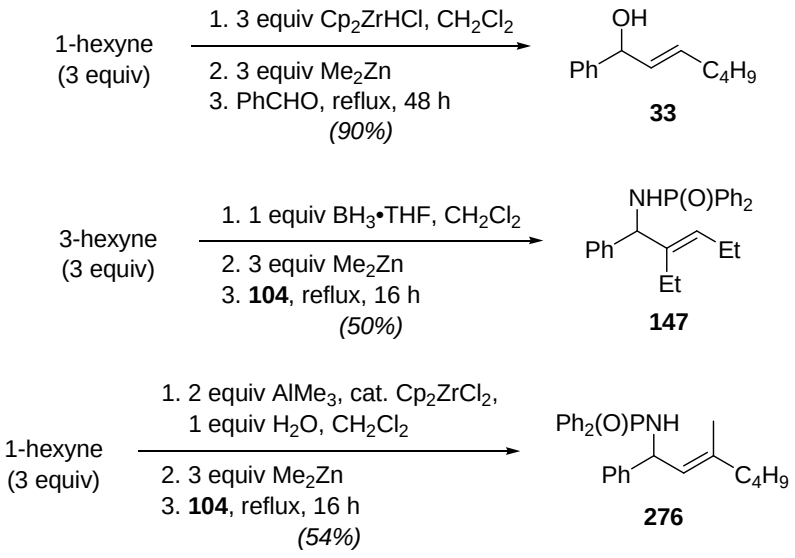


Figure 5. Proposed mechanism for formation of *C*-cyclopropylalkylamide **257**.

No cyclopropane was formed in CH_2Cl_2 at reflux if the aldimine **104** was replaced with benzaldehyde, or if the alkenylzinc species was generated by a hydroboration, B-Zn trans-metalation[216] (even in the presence of CH_2I_2, see Scheme 52) or carboalumination, Al-Zn transmetalation strategy (Scheme 48). Simmons-Smith cyclopropanation of allylic phosphinamide **146** afforded **257** as a 71:29 (*anti*:*syn*) mixture of diastereomers, and allylic sulfonamide **91** afforded **263** as an 81:19 (*anti*:*syn*) mixture of diastereomers. In both cases the diastereoselectivity was significantly lower than for the one-pot alkenylzirconocene addition/cyclopropanation. Thus, both the zirconocene complex and the aldimine may play a role in the reaction mechanism.



Scheme 48. Unsuccessful attempts to obtain cyclopropanation products in aldehyde or imine additions.

The high level of diastereoselectivity for *anti*-**257** can be rationalized using the allylic ether-directed cyclopropanation model[a] (Figure 6). Transition state **III**, normally invoked to explain *syn*-selective allylic alcohol directed cyclopropanation, minimizes allylic $A^{1,3}$ strain. Transition state **IV** instead minimizes steric interactions of the phenyl substituent with the bulky phosphinoyl protecting group on nitrogen. The zirconocene complex could act as a Lewis acid, activating the halomethyl zinc carbenoid, and forming a significantly larger cyclopropanation reagent *via* a bridged Zr-Zn complex,[217] which increases *anti*-selectivity compared to the (Zr-free) cyclopropanations of allylic amides **91** and **146**.

The isolated yield of allylic amide **276**, prepared by carboalumination/Al-Zn trans-metalation/imine addition was improved to 73% using the optimized addition conditions (toluene, room temperature), and the one-pot aldimine vinylation/cyclopropanation to form the corresponding 1,2,2-trisubstituted cyclopropane **278** was achieved using the optimized conditions for this transformation (Scheme 49). A mixture of **276** and **278** was obtained, and the cyclopropane **278** was formed as a 9:1 mixture of diastereomers. In this case, Me_2Zn was not necessary for cyclopropanation. Pure **278** was prepared by Simmons-Smith cyclopropanation of **276**, affording **278** as a single diastereomer. The relative stereochemistry of the isomer was

identical to that of the major diastereomer in the one-pot vinylation/cyclopropanation, and was assigned as *syn* based on literature precedent.

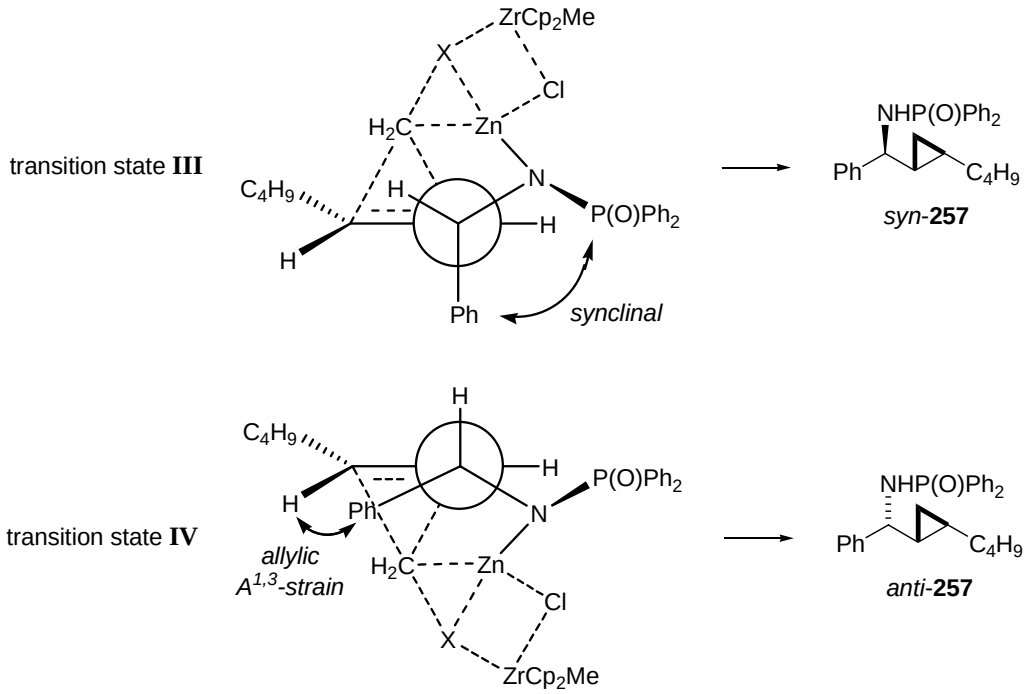
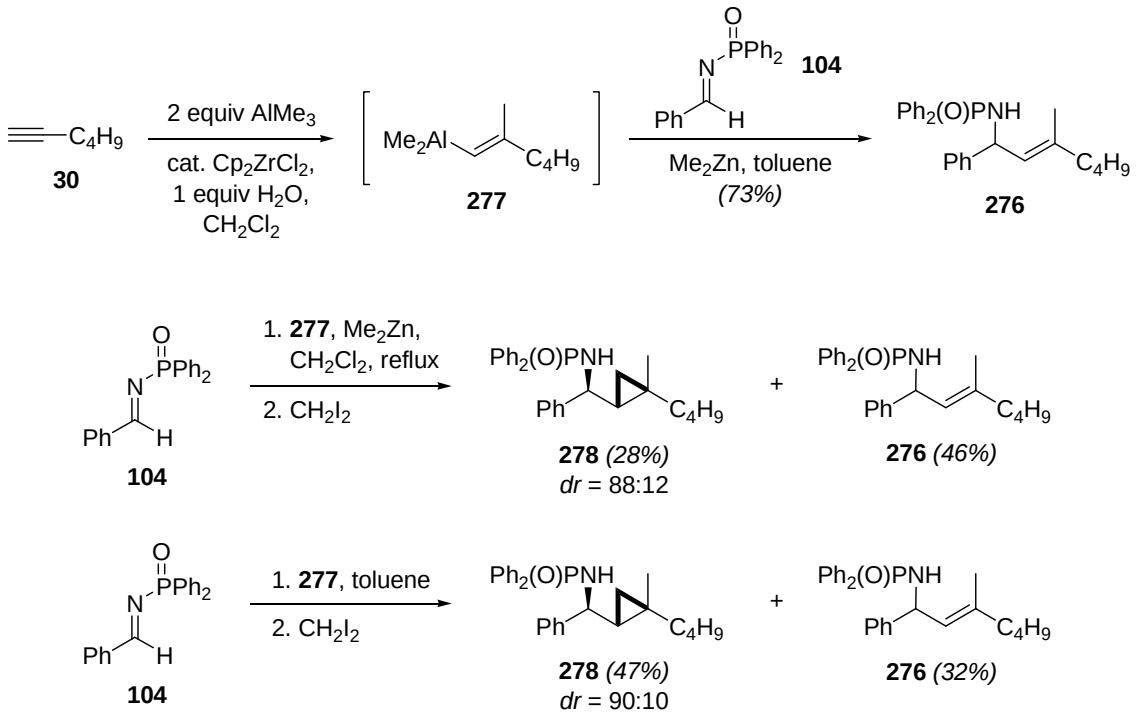


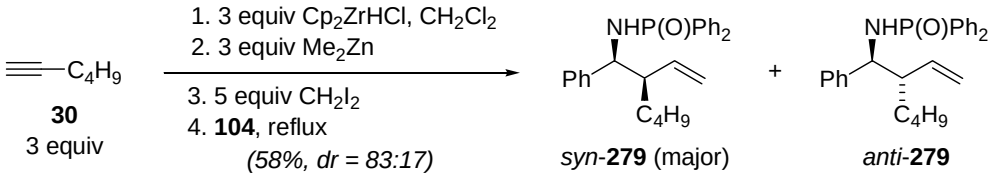
Figure 6. Transition state models for cyclopropanation of allylic amide **274**.

2.4. Synthesis of Homoallylic Amines[218]

Interestingly, the order of addition of reactants for the optimized *C*-cyclopropylalkylamine synthesis proved to be crucial for product formation. Addition of CH_2I_2 to the reaction mixture prior to imine **104** lead to a switch from the expected cyclopropylamide **257** to homoallylic amide **279**, in 58% yield and 5:1 diastereoselectivity, favoring the *syn*-isomer (Scheme 50).[219] This yield was slightly increased by lowering the temperature, but the effect on diastereoselectivity was minimal.



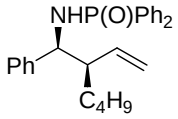
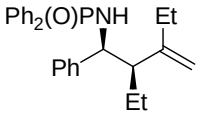
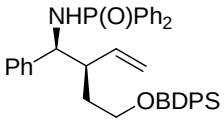
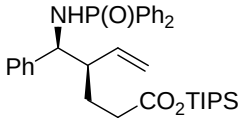
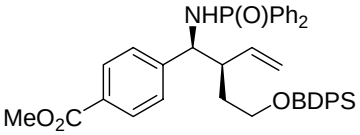
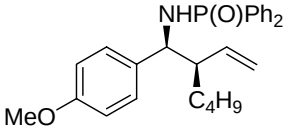
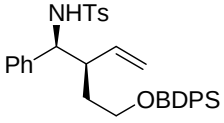
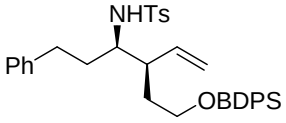
Scheme 49. Tandem carboalumination, aldimine additions with and without cyclopropanation.



Scheme 50. Unexpected formation of homoallylic amide **279**.

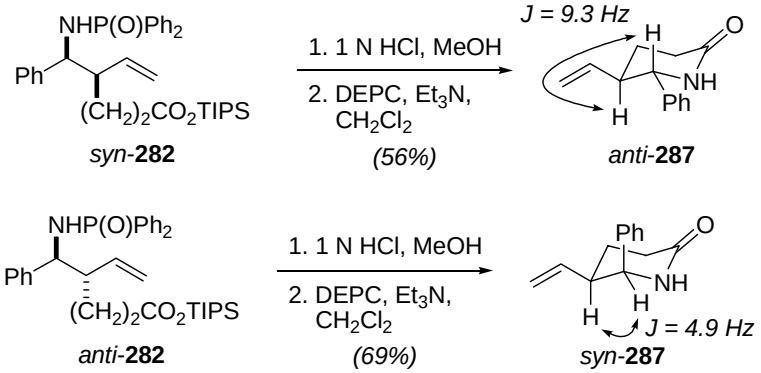
The reaction scope is illustrated in Table 13. Some functional groups on the alkyne segment, such as silyl ethers (Entry 3) did not interfere with the reaction; however, the use of silyl esters or internal alkynes resulted in both lower yield and reduced diastereoselectivity (Entries 4 and 2). Electron-donating and -withdrawing groups on the aldimine were tolerated and had no effect on product ratios (Entries 5 and 6). *N*-Tosylimines such as **90** and **166** were also suitable substrates, though **90** resulted in decreased diastereoselectivity (Entry 7), whereas **166** provided the homoallylated product **286** in excellent diastereoselectivity. Trace amounts of the corresponding *C*-cyclopropylalkylamines (e.g. **257** for Entry 1) were the only identifiable side products.

Table 13. Synthesis of homoallylic amines.

Entry	Alkyne	Aldimine	Homoallylic Amide[a,b]	Yield (%)[c]	*dr*[d]
1	1-hexyne (**30**)	**104**	 **279**	71	85:15
2	3-hexyne	**104**	 **280**	49	75:25
3	**148**	**104**	 **281**	72	85:15
4	**150**	**104**	 **282**	48	62:38
5	**148**	**156**	 **283**	69	85:15
6	**30**	**158**	 **284**	79	83:17
7	**148**	**90**	 **285**	81	60:40
8	**148**	**166**	 **286**	87	>95:5

[a]Only the major isomer is shown. [b]Reaction conditions: (i) 3 equiv of Cp_2ZrHCl, 3 equiv of alkyne, CH_2Cl_2, rt, 10 min; (ii) 4 equiv of Me_2Zn, CH_2Cl_2, -78 °C, 5 min; (iii) 5 equiv CH_2I_2, 1 equiv of aldimine, CH_2Cl_2, rt, 2-12 h. [c]Yields of isolated products are based on aldimines. [d]Determined by ^1H NMR analysis of the crude reaction mixture.

The assignment of the relative stereochemistry of these addition products was first based on the coupling constant analysis of lactams **287**, formed by hydrolysis and cyclization of homoallylic amides **282** (Scheme 51), and later confirmed by an X-ray analysis of *anti*-**287** (Appendix D). ^{1}H coupling constants of *anti*- and *syn*-**287** were characteristic for 1,2-diaxial and gauche relationships and were in good agreement with literature values.[220]



Scheme 51. Assignment of homoallylic amine stereochemistry.

A rationalization of the formation of the homoallylic product is shown in Figure 7. First, hydrozirconation of 1-hexyne followed by transmetalation with Me_2Zn afforded alkenylzinc **31**. Rapid reaction of **31** with CH_2I_2 formed, after [1,2]-shift, allylic zinc **289**, which added to aldimine **104** to form the observed homoallylic amide **279**.[221] A similar vinyl zinc to allyl zinc homologation mechanism was proposed by Marek and co-workers in their four-component coupling of alkynyl sulfoxides, organocopper reagents, electrophiles (aldehydes or aldimines) and bis(iodomethyl)zinc.[222] A closed transition state is likely for this reaction and minimization of allylic strain explains the preference for *syn*-configuration. Indirect support for a preferred cyclic transition state came from the dependence of the diastereoselectivity on the nature of the pseudoaxial imine substituents: the bulkier aromatic aldimines significantly eroded *syn*-selectivity versus an aliphatic chain (Table 13, Entries 7 and 8). Attempts to prepare the analogous homoallylic alcohols by replacing aldimines with aldehyde substrates were unsuccessful, and furthermore, efforts to prepare **280** using a B-Zn transmetalation strategy have also failed (Scheme 52). In either case, only allylic products were formed, and thus once again both the aldimine and a zirconocene complex may be important in the mechanism.

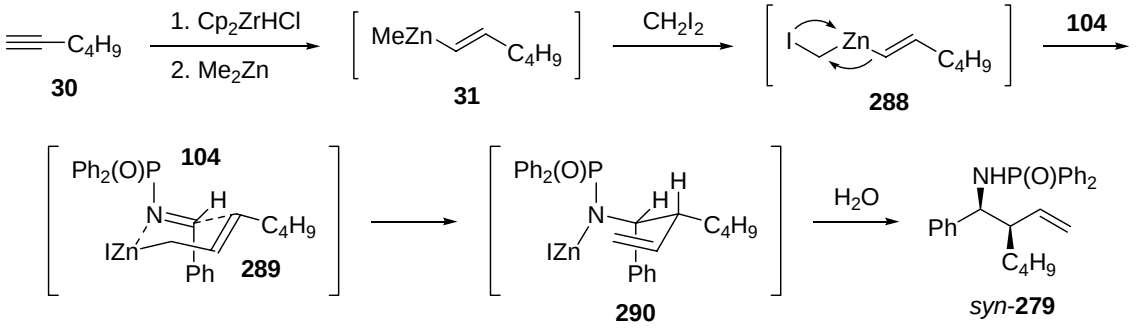
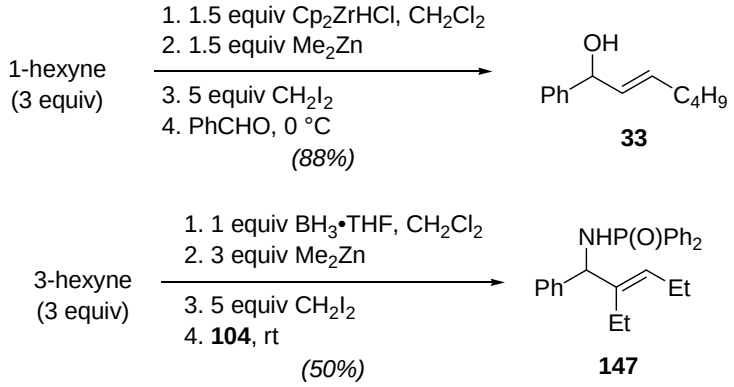


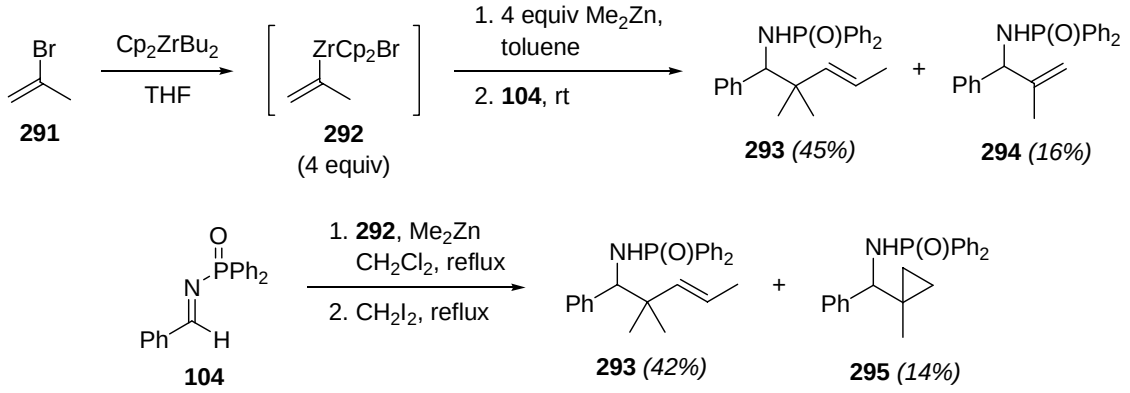
Figure 7. Proposed mechanism for formation of homoallylic amide *syn*-**279**.



Scheme 52. Unsuccessful one-pot vinylzinc homologation/electrophile allylation.

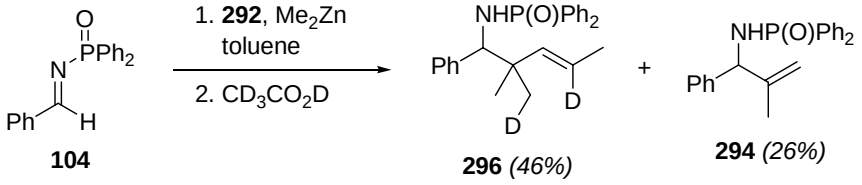
2.5. Application of an Alternate Preparation of Alkenylzirconocenes

Application of Takahashi's protocol for generating vinylzirconocenes (oxidative insertion of Cp_2Zr into a vinyl halide) to the optimized reaction conditions developed for allylic amide, *C*-cyclopropylalkylamine and homoallylic amide syntheses produced yet another unexpected result. Upon addition of Me_2Zn to vinylzirconocene **292**, followed by imine **104**, homoallylic amide **293** was the major product isolated, not the expected allylic amide **294** (Scheme 53). A similar result was obtained when CH_2I_2 was added (last) to the reaction mixture. Again homoallylic amide **293** was the major product formed, with cyclopropane **295** isolated in only 14% yield.



Scheme 53. Allylic amine and amino cyclopropane syntheses using Takahashi's protocol.

Mechanistic insight was obtained by quenching the reaction mixture with deuterated acetic acid (Scheme 54). In this case, bis-deuterated homoallylic amide **296** was isolated, in a very similar yield to **293**.



Scheme 54. Effect of a deuterium quench on the unexpected homoallylic amide **293**.

The bis-deuterated product **296** supported a zirconocycle precursor; a possible mechanism is shown in Figure 8. Oxidative insertion of Cp_2Zr into 2-bromopropene afforded alkenylzirconocene **292**. Ligand exchange on **292** with a second equivalent of Cp_2ZrBu_2 resulted in **297**, which could eliminate butane to form propyne complexed to Cp_2Zr (**298**). Alternatively ligand exchange could have occurred with Me_2Zn, followed by elimination of methane. Takahashi and co-workers have postulated this type of mechanism, by purposely treating **292** with a second equivalent of Cp_2ZrBu_2.[223] In their case, bis-zirconocene complex **300** was isolated and characterized. In the present case, however, addition of Me_2Zn and imine **104** to the reaction mixture could result in oxidative cyclization of the propyne-Cp_2Zr complex **298** and allylic amide **302** (formed by a Zr-Zn transmetalation on **292** or **297**, followed by addition to imine **104**). Deuterolysis of both C-Zr bonds of zirconacycle **303** would give the product with

correct deuterium substitution. Attempts to optimize or minimize the yield of **293** were unsuccessful, as were attempts to intercept the proposed mechanism with external alkynes.

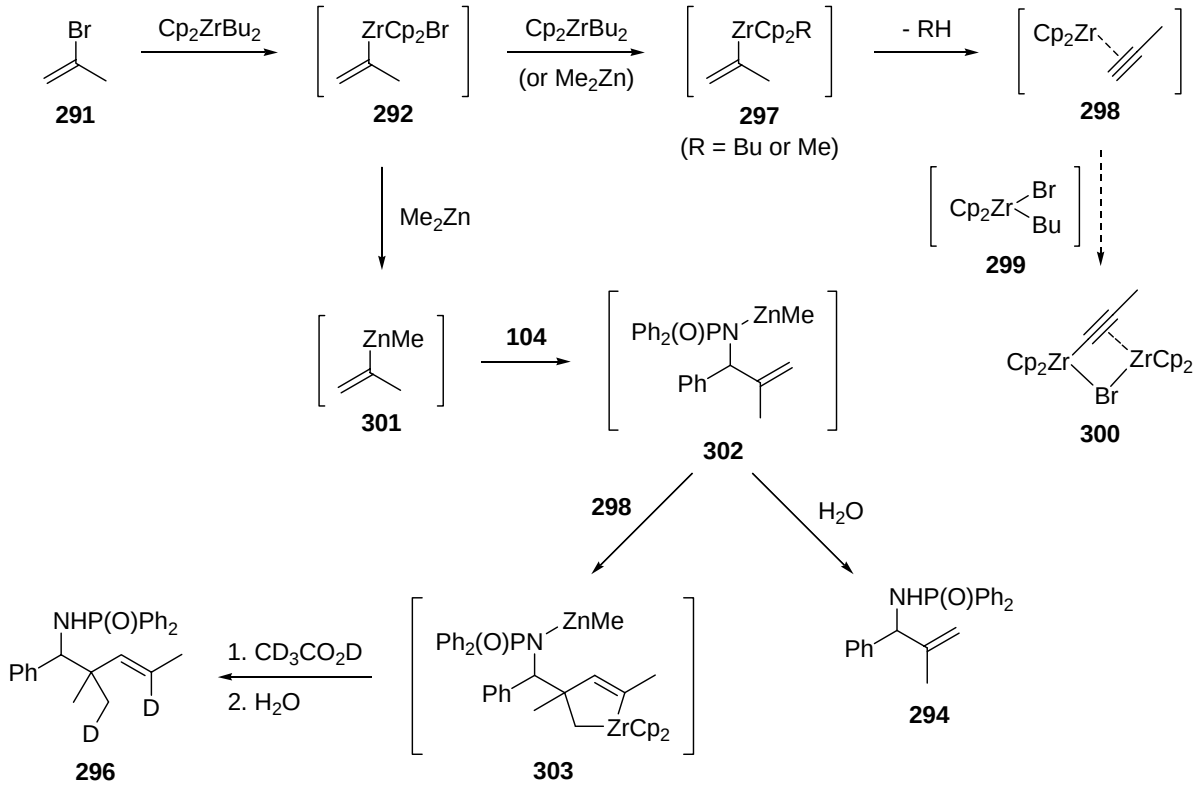
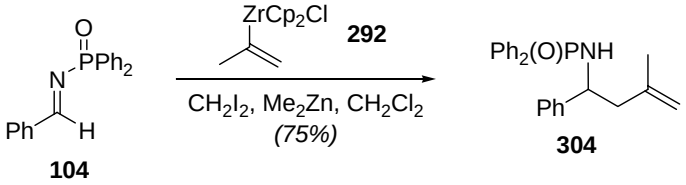


Figure 8. Proposed mechanism for formation of homoallylic amide **296**.

Under the optimized homoallylic amide reaction conditions shown in Table 13, **304** was formed in 75% yield, and no trace of **293** was detected in the reaction mixture (Scheme 55).



Scheme 55. Homoallylic amine synthesis using Takahashi's protocol.

3. Conclusions

The Zr-Zn transmetalation, aldehyde addition methodology developed in the Wipf group has been extended to the synthesis of allylic amines.[b] The use of toluene as a reaction solvent was required to obtain high yields and low reaction times. *N*-phosphinoyl-, *N*-sulfonoyl-, and *N*-carbamoylimines were excellent substrates for this transformation.

Many chiral ligands were tested for asymmetric catalysis, but minimal *ee* was achieved. A successful asymetric synthesis of allylic amines by alkenylzirconocene addition to imines will likely require conditions where transmetalation must take place with a chiral organometallic complex that will subsequently add to the imine or imine derivative without a significant decrease in reaction rate. No such conditions were found in this study.

A novel three-component *C*-cyclopropylalkylamine synthesis was discovered while attempting to perform the allylic amine synthesis in CH_2Cl_2. The mechanism of this transformation is not fully understood, however this is the first reported example of a high-yielding Simmons-Smith cyclopropanation with CH_2Cl_2 as the carbene precursor. This reaction was optimized by adding CH_2I_2 to the reaction mixture once all imine was consumed. Addition of CH_2I_2 prior to imine substrate resulted in homoallylic amine formation.

Takahashi's alkenylzirconocene protocol was applied to the allylic amine, *C*-cyclopropylalkylamine and homoallylic amine syntheses, allowing formation of products regioisomeric to those derived from hydrozirconation of terminal alkynes. A novel homoallylic amide was formed, believed to result from a zirconacyclopentene intermediate.

The amides prepared in Table 5, Table 12, and Table 13 were screened for acticvity against the estrogen receptor ERα. Cyclopropane **261** was found to be an antagonist comparable to tamoxifen (the first clinically successful antiestrogen) of 17β-estradiol (E2)-induced transcription (IC_{50} of 11 μM) in cell based and protein-ligand displacement assays.

In summary, the multi-component reaction of alkenylzirconocenes, imines, Me_2Zn and CH_2I_2 can form three different amide products, depending simply on the order of addition of reagents (Figure 9). Due to the functional group tolerance of both Zr and Zn chemistry, libraries of nitrogen-containing alkenes and cyclopropanes with many common functional groups can be rapidly prepared using inexpensive starting materials.

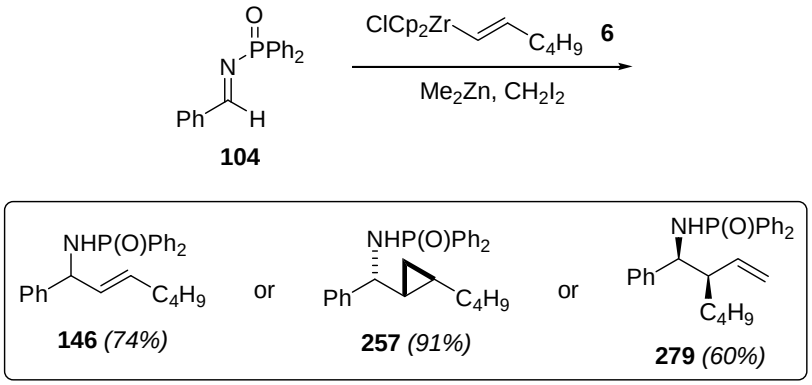


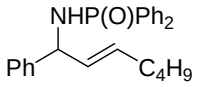
Figure 9. Diversity-oriented synthesis[224] of imine addition products.

4. Experimental Part

All moisture-sensitive reactions were performed using syringe-septum cap techniques under an N_2 or Ar atmosphere and all glassware was dried in an oven at 140 °C for 1 h prior to use. Reactions carried out at -78 °C employed a CO_2-acetone bath. THF was distilled over sodium/benzophenone ketyl, and CH_2Cl_2, toluene and Et_3N were distilled from CaH_2. Me_2Zn, Me_3Al, $TsNH_2$, CH_2I_2, *N*,*N*-dimethylurea, $Pd(OAc)_2$, dppf, and 2-bromobiphenyl were purchased from Aldrich Company. Cp_2ZrCl_2 was purchased from Boulder Scientific. (*R*,*R*)-DIOP (**215**) was purchased from Strem Chemical. Cp_2ZrHCl,[225] CH_3CHI_2,[226] *P*,*P*-diphenylphosphin-amide, imines **90**, **104**, **158**, **168**,[227] **170**, **176**,[228] **177**,[229] **178**,[230] **197**, and **199**, alkyne **148**, allylic phosphinamide **172**,[231] and ligands **55**, **56**, and **181**,[232] were prepared according to literature procedures.

Reactions were monitored by TLC analysis (EM Science pre-coated silica gel 60 F_{254} plates, 250 μm layer thickness) and visualization was accomplished with a 254 nm UV light and by staining with a PMA solution (5 g of phosphomolybdic acid in 100 mL of 95% EtOH), *p*-anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 2 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95% EtOH), Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}$•4 H_2O and 0.2 g of $Ce(SO_4)_2$ in 100 mL of a 3.5 N H_2SO_4 solution) or a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution). Flash chromatography on SiO_2 or deactivated SiO_2 (1% Et_3N in mobile phase) was used to purify the crude reaction mixtures.

Melting points were determined using a Laboratory Devices Mel-Temp II. Infrared spectra were determined on a Nicolet Avatar 360 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were obtained on a Bruker Avance 300 instrument in $CDCl_3$ unless otherwise noted. Chemical shifts were reported in parts per million with the residual solvent peak used as an internal standard. ^1H NMR spectra were run at 300 MHz and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet), number of protons, and coupling constant(s). ^{13}C NMR spectra were run at 76 MHz using the proton-decoupled pulse sequence with a d_1 of 4 s, and are tabulated by observed peak for compounds **146**-**148**, **151**, **153**, **156**, **157**, **159**-**165**, **249**, **257**-**262**, **266**, **267**, **276**, **278**-**284**, **293**-**296**, and **304**, and by chemical shift for all other compounds. Mass spectra were obtained on a Micromass Autospec double focusing instrument.



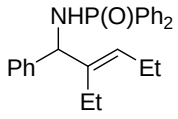
146

(*E*)-*N*-(1-Phenylhept-2-enyl)-*P*,*P*-diphenylphosphinamide (146). General Protocol A. A suspension of 208 mg (0.807 mmol) of Cp_2ZrHCl in 2 mL of CH_2Cl_2 was treated with 105 μL (0.914 mmol) of 1-hexyne, stirred for 5 min, and concentrated *in vacuo*. A solution of the residue in 2 mL of toluene was cooled to -78 °C, treated with 380 μL (0.760 mmol) of Me_2Zn (2.0 M solution in toluene), warmed to room temperature over a period of 5 min and cannulated into a suspension of 155 mg (0.508 mmol) of imine **104** in 2 mL of toluene. The mixture was stirred at room temperature for 2 h, quenched with saturated NH_4Cl, diluted with EtOAc, washed with 1 N HCl and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on deactivated SiO_2 (1:9, hexanes/EtOAc containing 1% Et_3N) to yield 151 mg (76%) of **146** as a colorless solid: mp 139-140 °C (EtOAc/hexane); IR (KBr) 3127, 2952, 2922, 2859, 1456, 1437, 1194, 1182, 1121, 1109, 722, 695 cm^{-1}; ^1H NMR δ 8.00-7.93 (m, 2 H), 7.89-7.82 (m, 2 H), 7.55-7.23 (m, 11 H), 5.69 (ddt, 1 H, *J* = 15.3, 6.2, 1.2 Hz), 5.53 (dtd, 1 H, *J* = 15.3, 6.6, 1.1 Hz), 4.83 (td, 1 H, *J* = 9.4, 6.4 Hz), 3.34 (dd, 1 H, *J* = 9.4, 6.2 Hz), 2.01 (q, 2 H, *J* = 6.4 Hz), 1.34-1.26 (m, 4 H), 0.90 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR δ 143.03, 142.96, 133.73, 133.39, 132.45, 132.29, 132.17, 132.06, 132.01, 131.67, 128.44, 128.37, 128.21, 127.10, 126.92, 56.87, 31.77, 31.12, 22.19, 13.88; EIMS *m/z* 389 (M^+, 15), 332 (19), 306 (25), 216 (98), 201 (92), 188 (100), 172 (35), 143 (55), 129 (87), 115 (35), 91 (33), 77 (60); HRMS (EI) *m/z* calcd for $C_{25}H_{28}NOP$ 389.1909, found 389.1906.

Representative attempted asymmetric preparation of 146 (catalytic ligand). A suspension of 77.0 mg (0.299 mmol) of Cp_2ZrHCl in 2 mL of CH_2Cl_2 was treated with 40.0 μL (0.348 mmol) of 1-hexyne, stirred for 5 min, and concentrated *in vacuo*. A solution of the residue in 1 mL of toluene was cooled to -78 °C, treated with 150 μL (0.300 mmol) of Me_2Zn (2.0 M solution in toluene), warmed to room temperature over a period of 5 min and cannulated into a suspension of 76.0 mg (0.249 mmol) of imine **104** and 7.0 mg (0.026 mmol) of ligand **55** in 1 mL of toluene. The mixture was stirred at room temperature for 16 h, quenched with saturated NH_4Cl, diluted with EtOAc, washed with H_2O, saturated $NaHCO_3$ and brine, dried ($MgSO_4$), filtered through Florisil, and concentrated *in vacuo*. The residue was chromatographed on deactivated SiO_2 (1:9, hexanes/EtOAc containing 1% Et_3N) to yield 63 mg (65%) of

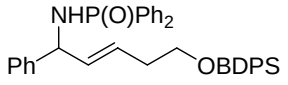
146 as a colorless solid. The enantioselectivity was measured by chiral HPLC using a Chiracel OD column (12% *i*-PrOH in hexanes, 1.0 mL/min, R_T = 5.1 and 6.9 min): 2% *ee*.

Representative attempted asymmetric preparation of 146 (stoichiometric ligand). A suspension of 85.0 mg (0.330 mmol) of Cp_2ZrHCl in 1 mL of CH_2Cl_2 was treated with 40.0 μL (0.348 mmol) of 1-hexyne, stirred for 5 min, and concentrated *in vacuo*. A solution of the residue in 1 mL of toluene was cannulated into a suspension, cooled to -78 °C, of 50.0 mg (0.164 mmol) of imine **104**, 44.0 mg (0.163 mmol) of ligand **55**, and 250 μL (0.500 mmol) of Me_2Zn (2.0 M solution in toluene) in 1 mL of toluene. The mixture was stirred at 10 °C for 24 h, quenched with saturated NH_4Cl, diluted with EtOAc, washed with 1 N HCl and brine, dried ($MgSO_4$), filtered through Florisil, and concentrated *in vacuo*. The residue was chromatographed on deactivated SiO_2 (1:4, hexanes/EtOAc containing 1% Et_3N) to yield 48 mg (75%) of **146** as a colorless solid. The enantioselectivity was measured by chiral HPLC using a Chiracel OD column (12% *i*-PrOH in hexanes, 1.0 mL/min, R_T = 5.1 and 6.8 min): 23% *ee*.



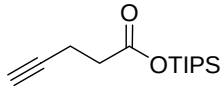
147

(*E*)-*N*-(2-Ethyl-1-phenylpent-2-enyl)-*P*,*P*-diphenylphosphinamide (147). According to the General Protocol A, 205 mg (0.795 mmol) of Cp_2ZrHCl, 105 μL (0.924 mmol) of 3-hexyne, 380 μL (0.760 mmol) of Me_2Zn (2.0 M solution in toluene), and 153 mg (0.501 mmol) of imine **104** (4 h reaction time) afforded 140 mg (72%) of **147** as a colorless solid: mp 129-130 °C (EtOAc/hexane); IR (KBr) 3165, 2959, 2931, 2872, 1436, 1187, 1179, 1107, 727, 696 cm^{-1}; ^1H NMR δ 8.00-7.93 (m, 2 H), 7.91-7.83 (m, 2 H), 7.54-7.21 (m, 11 H), 5.56 (t, 1 H, *J* = 7.2 Hz), 4.76 (t, 1 H, *J* = 10.8 Hz), 3.29 (dd, 1 H, *J* = 10.1, 6.2 Hz), 2.19-2.07 (m, 3 H), 1.77 (dq, 1 H, *J* = 14.5, 7.5 Hz), 1.06 (t, 3 H, *J* = 7.5 Hz), 0.73 (t, 3 H, *J* = 7.6 Hz); ^{13}C NMR δ 142.53, 142.48, 140.94, 140.87, 133.50, 133.40, 132.49, 132.36, 132.13, 132.01, 131.80, 131.75, 131.70, 131.66, 128.56, 128.34, 128.20, 128.16, 127.44, 127.04, 59.11, 21.86, 20.84, 14.43, 13.49; EIMS *m/z* 389 (M^+, 15), 306 (20), 218 (55), 201 (88), 188 (100), 143 (33), 129 (15), 91 (27), 77 (29); HRMS (EI) *m/z* calcd for $C_{25}H_{28}NOP$ 389.1909, found 389.1905.



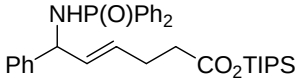
149

(*E*)-*N*-{5-[(*tert*-Butyldiphenylsilyl)oxy]-1-phenylpent-2-enyl}-*P*,*P*-diphenylphosphinamide (149). According to the General Protocol A, 205 mg (0.795 mmol) of Cp_2ZrHCl, 300 mg (0.972 mmol) of alkyne **148**, 380 μL (0.760 mmol) of Me_2Zn (2.0 M solution in toluene), and 153 mg (0.501 mmol) of imine **104** (12 h reaction time) afforded 226 mg (73%) of **149** as a colorless solid: mp 118-119 °C (EtOAc/hexane); IR (KBr) 3131, 3052, 2928, 2857, 1457, 1438, 1428, 1192, 1111, 1088, 740, 723, 698 cm^{-1}; ^1H NMR δ 8.00-7.93 (m, 2 H), 7.90-7.83 (m, 2 H), 7.70-7.67 (m, 4 H), 7.52-7.25 (m, 17 H), 5.80 (dd, 1 H, *J* = 15.4, 6.0 Hz), 5.57 (dtd, 1 H, *J* = 15.3, 6.8, 1.2 Hz), 4.86 (td, 1 H, *J* = 9.4, 6.2 Hz), 3.68 (t, 2 H, *J* = 6.6 Hz), 3.33 (dd, 1 H, *J* = 9.6, 6.3 Hz), 2.32 (q, 2 H, *J* = 6.6 Hz), 1.07 (s, 9 H); ^{13}C NMR δ 142.63, 142.56, 135.47, 133.77, 133.69, 133.58, 133.29, 132.25, 132.19, 132.12, 132.06, 131.86, 131.74, 131.69, 131.65, 131.58, 129.50, 128.69, 128.43, 128.37, 128.20, 127.55, 127.15, 126.99, 63.27, 56.69, 35.48, 26.75, 19.11; EIMS *m/z* 600 ($[M\text{-}CH_3]^+$, 3), 558 (82), 201 (24), 199 (32), 143 (24), 91 (20), 77 (37), 61 (100); HRMS (EI) *m/z* calcd for $C_{38}H_{39}NO_2PSi$ [M-CH_3] 600.2488, found 600.2465.



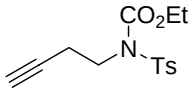
150

***O*-Triisopropylsilyl-4-pentynoate (150).** According to a literature procedure, a solution of 1.17 g (11.9 mmol) of 4-pentynoic acid in 25 mL of CH_2Cl_2 was treated with 2.29 g (11.9 mmol) of TIPS-Cl and 0.812 g (11.9 mmol) of imidazole. The mixture was stirred at room temperature for 2 h, filtered through Celite, washed with 1 N HCl and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was Kugelrohr distilled to yield 3.04 g (100%) of **150** as a colorless oil: IR (neat) 3315, 2945, 2870, 1722, 1466, 1372, 1268, 1191, 1068, 1015 cm^{-1}; ^1H NMR δ 2.62-2.57 (m, 2 H), 2.52-2.45 (m, 2 H), 1.96 (t, 1 H *J* = 2.6 Hz), 1.35-1.23 (m, 3 H), 1.07 (d, 18 H, *J* = 7.2 Hz); ^{13}C NMR δ 171.64, 82.71, 68.90, 34.90, 17.71, 14.67, 11.87; EIMS *m/z* 211 ($[M\text{-}C_3H_7]^+$, 100), 155 (18), 131 (22), 103 (47); HRMS (EI) *m/z* calcd for $C_{11}H_{19}O_2Si$ [M-C_3H_7] 211.1154, found 211.1158.



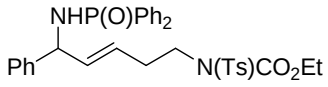
151

(*E*)-*O*-Triisopropylsilyl-6-(diphenylphosphinyl)amino-6-phenylhex-4-enoate (151). According to the General Protocol A, 260 mg (1.01 mmol) of Cp_2ZrHCl, 285 mg (1.10 mmol) of alkyne **150**, 500 μL (1.00 mmol) of Me_2Zn (2.0 M solution in toluene), and 153 mg (0.501 mmol) of imine **104** (12 h reaction time) afforded 184 mg (65%) of **151** as a colorless oil: IR (neat) 3167, 2945, 2868, 1718, 1464, 1437, 1186, 1123, 1110 cm^{-1}; ^1H NMR δ 7.94-7.77 (m, 4 H), 7.50-7.19 (m, 11 H), 5.70 (dd, 1 H, *J* = 15.3, 6.2 Hz), 5.51 (dt, 1 H, *J* = 15.5, 5.8 Hz), 4.79 (dt, 1 H, *J* = 9.2, 6.6 Hz), 3.30 (dd, 1 H, *J* = 9.1, 6.1 Hz), 2.53-2.23 (m, 4 H), 1.30-1.10 (m, 3 H), 1.02 (d, 18 H, *J* = 7.2 Hz); ^{13}C NMR δ 172.81, 142.65, 132.88, 132.28, 132.19, 132.07, 131.74, 130.40, 128.53, 128.43, 128.27, 127.27, 126.93, 56.90, 35.11, 27.58, 17.72, 11.86; EIMS *m/z* 561 (M^+, 8), 518 (40), 361 (41), 346 (25), 330 (58), 301 (17), 218 (52), 201 (100), 158 (20), 143 (24), 128 (29), 115 (37), 103 (41); HRMS (EI) *m/z* calcd for $C_{33}H_{44}NO_3PSi$ 561.2828, found 561.2849.



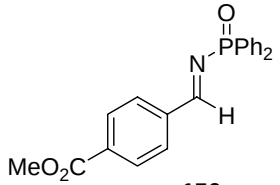
152

***O*-Ethyl-*N*-but-3-ynyl-*N*-[(4-methylphenyl)sulfonyl]carbamate (152).** According to a literature procedure,[233] a solution of 5.39 g (20.5 mmol) of PPh_3 and 2.50 g (10.3 mmol) of $TsNHCO_2Et$[234] in 100 mL of THF was treated with 520 μL (6.85 mmol) of 3-butyn-1-ol and 2.70 mL (17.1 mmol) of DEAD, stirred at room temperature for 16 h, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (80:20, hexanes/EtOAc) to yield 1.95 g (96%) of **152** as a colorless solid: mp 63-65 °C (EtOAc/hexane); IR (KBr) 3307, 2993, 2941, 2121, 1734, 1353, 1329, 1268, 1168, 1028, 964, 866, 812, 769, 741, 657 cm^{-1}; ^1H NMR δ 7.83 (d, 2 H, *J* = 8.4 Hz), 7.30 (d, 2 H, *J* = 8.1 Hz), 4.13 (q, 2 H, *J* = 7.1 Hz), 4.00 (dd, 2 H, *J* = 8.0, 7.0 Hz), 2.64 (td, 2 H, *J* =7.5, 2.7 Hz), 2.42 (s, 3 H), 2.02 (t, 1 H, *J* = 2.7 Hz), 1.18 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 152.06, 144.67, 136.44, 129.31, 128.37, 80.17, 70.53, 63.52, 45.26, 21.62, 19.91, 13.96; EIMS *m/z* 295 (M^+, 4), 256 (31), 184 (58), 155 (100), 91 (89); HRMS (EI) calcd for $C_{14}H_{17}NO_4S$ 295.0878, found 295.0892.



153

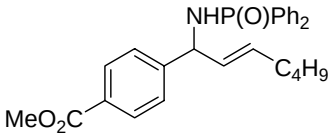
(*E*)-*O*-Ethyl-*N*-{5-[(diphenylphosphinyl)amino]-5-phenylpent-3-enyl}-*N*-[(4-methylphenyl)sulfonyl]carbamate (153). According to the General Protocol A, 205 mg (0.795 mmol) of Cp_2ZrHCl, 253 mg (0.857 mmol) of alkyne **152**, 380 μL (0.760 mmol) of Me_2Zn (2.0 M solution in toluene), and 153 mg (0.501 mmol) of imine **104** (12 h reaction time) afforded 177 mg (59%) of **153** as a colorless solid: mp 159-160 °C (EtOAc/hexane); IR (KBr) 3168, 3064, 2960, 2871, 1736, 1436, 1370, 1359, 1277, 1186, 1160, 1125, 970, 726, 702, 679 cm^{-1}; ^1H NMR δ 7.99-7.92 (m, 2 H), 7.89-7.80 (m, 4 H), 7.53-7.44 (m, 4 H), 7.41-7.35 (m, 2 H), 7.33-7.24 (m, 7 H), 5.85 (dd, 1 H, *J* = 15.4, 5.8 Hz), 5.54 (dtd, 1 H, *J* = 15.4, 7.1, 1.3 Hz), 4.84 (td, 1 H, *J* = 9.6, 6.0 Hz), 4.09 (q, 2 H, *J* = 7.1 Hz), 3.85 (t, 2 H, *J* = 7.3 Hz), 3.52 (dd, 1 H, *J* = 9.5, 6.8 Hz), 2.50-2.44 (m, 2 H), 2.44 (s, 3 H), 1.15 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 152.08, 144.97, 142.35, 142.28, 136.69, 135.19, 135.13, 133.62, 133.15, 132.28, 132.15, 132.03, 131.91, 131.76, 131.72, 131.69, 131.66, 131.43, 129.19, 128,43, 128.35, 128.26, 128.20, 127.47, 127.19, 127.00, 63.24, 56.47, 46.40, 32.63, 21.54, 13.92; EIMS *m/z* 602 (30), 401 (63), 358 (25), 346 (41), 332 (15), 230 (31), 218 (17), 201 (100), 158 (50), 155 (30), 91 (53), 77 (19); HRMS (EI) calcd for $C_{33}H_{35}N_2O_5PS$ 602.2004, found 602.2004.



156

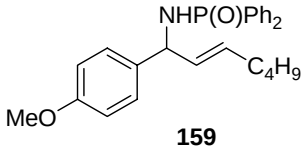
Methyl 4-[(diphenylphosphinylimino)methyl]benzoate (156). General Protocol B. According to a literature procedure, a suspension of 1.50 g (6.91 mmol) of *P*,*P*-diphenylphosphinamide, 1.25 g (7.61 mmol) of methyl 4-formylbenzoate, and 3.00 mL (20.8 mmol) of Et_3N in 15 mL of CH_2Cl_2 was cooled to 0 °C, treated dropwise with a solution of 3.50 mL (3.50 mmol) of $TiCl_4$ (1.0 M solution in CH_2Cl_2) in 5 mL of CH_2Cl_2 over 10 min, warmed to room temperature and stirred for 1 h. The mixture was poured into 150 mL of Et_2O,[235] stirred for 5 min, filtered through a pad of Florisil, and concentrated *in vacuo*. The residue was precipitated from CH_2Cl_2 with hexanes to yield 1.19 g (47%) of **156** as a colorless solid: mp 143-145 °C (CH_2Cl_2/hexanes); IR (KBr) 3226, 3060, 3037, 1725, 1613, 1568, 1438, 1280, 1203, 1127, 1107,

861, 834, 766, 750, 729, 697 cm^{-1}; ^1H NMR δ 9.34 (d, 1 H, *J* = 31.7 Hz), 8.15-8.12 (m, 2 H), 8.06-8.03 (m, 2 H), 7.96-7.89 (m, 4 H), 7.48-7.36 (m, 6 H), 3.91 (s, 3 H); ^{13}C NMR δ 172.62, 172.52, 166.09, 139.22, 138.89, 134.15, 133.20, 131.91, 131.88, 131.76, 131.63, 131.53, 131.41, 129.95, 129.85, 128.55, 128.38, 128.26, 52.40; EIMS *m/z* 363 (M^+, 24), 201 (100); HRMS (EI) *m/z* calcd for $C_{21}H_{18}NO_3P$ 363.1024, found 363.1018.



157

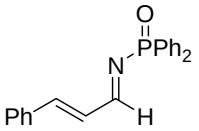
(*E*)-Methyl 4-{1-[(diphenylphosphinyl)amino]hept-2-enyl}benzoate (157). According to the General Protocol A, 103 mg (0.399 mmol) of Cp_2ZrHCl, 51.0 μL (0.444 mmol) of 1-hexyne, 190 μL (0.380 mmol) of Me_2Zn (2.0 M solution in toluene), and 94.0 mg (0.259 mmol) of imine **156** (1 h reaction time) afforded 97 mg (84%) of **157** as a colorless solid: mp 129-130 °C (EtOAc/hexane); IR (KBr) 3122, 2956, 2928, 2872, 1722, 1437, 1276, 1194, 1109, 724, 695 cm^{-1}; ^1H NMR δ 8.01-7.90 (m, 4 H), 7.85-7.78 (m, 2 H), 7.56-7.34 (m, 8 H), 5.68 (ddt, 1 H, *J* = 15.3, 6.2, 1.2 Hz), 5.51 (dtd, 1 H, *J* = 15.3, 6.6, 1.1 Hz), 4.87 (td, 1 H, *J* = 9.7, 6.3 Hz), 3.93 (s, 3 H), 3.42 (dd, 1 H, *J* = 9.4, 6.4 Hz), 2.01 (q, 2 H, *J* = 6.7 Hz), 1.34-1.24 (m, 4 H), 0.89 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR δ 166.83, 148.10, 148.04, 133.37, 133.18, 133.11, 132.26, 132.14, 132.02, 131.88, 131.83, 131.79, 131.66, 131.40, 131.08, 131.02, 129.77, 128.91, 128.47, 128.43, 128.31, 128.26, 126.98, 56.59, 52.03, 31.78, 31.05, 22.17, 13.86; EIMS *m/z* 447 (M^+, 3), 246 (15), 230 (21), 201 (21), 141 (19), 129 (35), 87 (100), 84 (45); HRMS (EI) *m/z* calcd for $C_{27}H_{30}NO_3P$ 447.1963, found 447.1961.



159

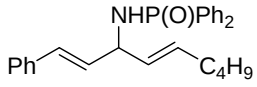
(*E*)-*N*-[1-(4-Methoxyphenyl)hept-2-enyl]-*P*,*P*-diphenylphosphinamide (159). According to the General Protocol A, 195 mg (0.756 mmol) of Cp_2ZrHCl, 95.0 μL (0.827 mmol) of 1-hexyne, 380 μL (0.760 mmol) of Me_2Zn (2.0 M solution in toluene), and 149 mg (0.444 mmol) of imine **158** (4 h reaction time) afforded 65 mg (35%) of **159** as a colorless oil: IR (thin film) 2957, 2929, 2871, 2836, 1604, 1511, 1439, 1251, 1175, 1127, 1035, 986, 755, 721, 697 cm^{-1}; ^1H NMR δ 7.95-7.78 (m, 4 H), 7.50-7.32 (m, 6 H), 7.24-7.19 (m, 2 H), 6.85-6.80 (m, 2 H),

5.63 (dd, 1 H, *J* = 15.3, 6.1 Hz), 5.48 (dtd, 1 H, *J* = 15.3, 6.7, 1.0 Hz), 4.74 (td, 1 H, *J* = 9.5, 6.1 Hz), 3.77 (s, 3 H), 3.20 (dd, 1 H, *J* = 9.2, 6.2 Hz), 2.00-1.93 (m, 2 H), 1.29-1.22 (m, 4 H), 0.86 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR δ 158.63, 135.27, 135.20, 133.73, 133.49, 132.33, 132.20, 132.07, 132.01, 131.84, 131.78, 131.74, 131.70, 131.66, 128.41, 128.24, 128.12, 113.95, 113.79, 56.32, 55.23, 31.79, 31.19, 22.23, 13.91; EIMS *m/z* 419 (M^+, 6), 336 (24), 218 (42), 202 (92), 173 (100), 159 (48); HRMS (EI) *m/z* calcd for $C_{26}H_{30}NO_2P$ 419.2014, found 419.2007.



160

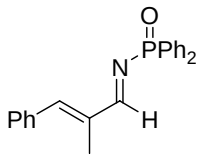
(2*E*)-*N*-(3-Phenylallylidene)-*P,P*-diphenylphosphinamide (160). According to the General Protocol B, 2.00 g (9.21 mmol) of *P,P*-diphenylphosphinamide, 1.50 mL (11.9 mmol) of *trans*-cinnamaldehyde, 4.00 mL (28.7 mmol) of Et_3N, and 600 μL (5.47 mmol) of $TiCl_4$ afforded 1.39 g (46%) of **160** as a colorless solid: mp 142-143 °C (CH_2Cl_2/hexanes); IR (KBr) 3065, 3020, 1629, 1591, 1438, 1207, 1125, 1106, 869, 802, 757, 727, 703, 694 cm^{-1}; ^{1}H NMR δ 9.04 (dd, 1 H, *J* = 31.7, 9.0 Hz), 7.93-7.86 (m, 4 H), 7.56-7.34 (m, 12 H), 7.10 (ddd, *J* = 15.8, 9.0, 2.1 Hz); ^{13}C NMR δ 174.83, 174.72, 150.57, 134.60, 133.69, 132.02, 131.72, 131.68, 131.55, 131.43, 130.75, 128.98, 128.79, 128.50, 128.41, 128.34, 128.22; EIMS *m/z* 331 (M^+, 7), 201 (48), 130 (100), 77 (52); HRMS (EI) *m/z* calcd for $C_{21}H_{18}NOP$ 331.1126, found 331.1114.



161

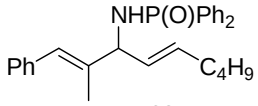
(*E*)-*N*-[1-(2-Phenylvinyl)hept-2-enyl]-*P,P*-diphenylphosphinamide (161). According to the General Protocol A, 200 mg (0.776 mmol) of Cp_2ZrHCl, 100 μL (0.870 mmol) of 1-hexyne, 750 μL (1.50 mmol) of Me_2Zn (2.0 M solution in toluene), and 165 mg (0.498 mmol) of imine **160** (4 h reaction time) afforded 57 mg (28%) of **161** as a colorless solid: mp 141-142 °C (Et_2O/hexane); IR (KBr) 3089, 2954, 2923, 2855, 1438, 1200, 1183, 1122, 1109, 965, 747, 723, 696 cm^{-1}; ^{1}H NMR δ 7.96-7.88 (m, 4 H), 7.52-7.37 (m, 6 H), 7.33-7.19 (m, 5 H), 6.42 (dd, 1 H, *J* = 15.9, 1.1 Hz), 6.23 (dd, 1 H, *J* = 15.4, 6.5 Hz), 5.60-5.57 (m, 2 H), 4.39-4.36 (m, 1 H), 3.01 (dd, 1 H, *J* = 9.5, 5.9 Hz), 2.04-1.98 (m, 2 H), 1.34-1.25 (m, 4 H), 0.88 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR δ 136.85, 133.81, 133.77, 132.59, 132.42, 132.39, 132.29, 132.26, 132.09, 132.05, 131.90,

131.40, 131.33, 130.78, 130.71, 130.35, 128.62, 128.57, 128.45, 127.65, 126.60, 54.96, 32.05, 31.36, 22.36, 14.06; EIMS *m/z* 415 (M^+, 26), 358 (55), 216 (48), 214 (100), 201 (83), 199 (32), 155 (43), 124 (22), 91 (37), 77 (34); HRMS (EI) *m/z* calcd for $C_{27}H_{30}NOP$ 415.2065, found 415.2105.



162

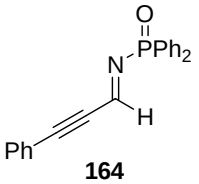
(2*E*)-*N*-(2-Methyl-3-phenylallylidene)-*P*,*P*-diphenylphosphinamide (162). According to the General Protocol B, 2.00 g (9.21 mmol) of *P*,*P*-diphenylphosphinamide, 1.50 mL (10.7 mmol) of α-methylcinnamaldehyde, 4.00 mL (28.7 mmol) of Et_3N, and 600 μL (5.47 mmol) of $TiCl_4$ afforded 1.47 g (46%) of **162** as a colorless solid: mp 153-154 °C (CH_2Cl_2/hexanes); IR (KBr) 3049, 3026, 2952, 2883, 1603, 1443, 1437, 1196, 1128, 1108, 1021, 887, 846, 754, 729, 706, 693 cm^{-1}; ^1H NMR δ 8.98 (d, 1 H, *J* = 31.2 Hz), 7.96-7.89 (m, 4 H), 7.49-7.34 (m, 11 H), 7.22 (s, 1 H), 2.28 (s, 3 H); ^{13}C NMR δ 177.91, 177.81, 148.09, 137.74, 137.40, 135.62, 134.16, 132.48, 131.61, 131.55, 131.42, 129.94, 129.07, 128.53, 128.45, 128.29, 12.43; EIMS *m/z* 345 (M^+, 43), 201 (85), 144 (100), 77 (75); HRMS (EI) *m/z* calcd for $C_{22}H_{20}NOP$ 345.1283, found 345.1278.



163

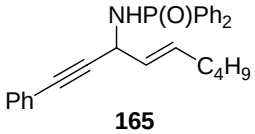
(*E*)-*N*-[1-(1-Methyl-2-phenylvinyl)hept-2-enyl]-*P*,*P*-diphenylphosphinamide (163). According to the General Protocol A, 195mg (0.756 mmol) of Cp_2ZrHCl, 100 μL (0.870 mmol) of 1-hexyne, 380 μL (0.760 mmol) of Me_2Zn (2.0 M solution in toluene), and 173 mg (0.501 mmol) of imine **162** (4 h reaction time) afforded 154 mg (72%) of **163** as a colorless oil: IR (thin film) 3176, 3054, 2954, 2927, 2855, 1437, 1192, 1124, 1109, 972, 916, 748, 724, 697 cm^{-1}; ^1H NMR δ 8.11-8.03 (m, 4 H), 7.65-7.53 (m, 6 H), 7.49-7.33 (m, 5 H), 6.50 (s, 1 H), 5.79 (dtd, 1 H, *J* = 15.3, 6.4, 1.0 Hz), 5.66 (dd, 1 H, *J* = 15.4, 5.7 Hz), 4.42 (td, 1 H, *J* = 9.4, 5.7 Hz), 3.28 (dd, 1 H, *J* = 9.2, 5.9 Hz), 2.19-2.13 (m, 2 H), 1.98 (s, 3 H), 1.68-1.41 (m, 4 H), 1.03 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 138.74, 138.68, 137.58, 133.78, 133.52, 132.52, 132.31, 132.19, 132.16, 132.07, 132.03, 131.79, 131.72, 130.36, 130.29, 128.86, 128.62, 128.52, 128.44, 128.38, 128.27,

128.21, 127.96, 126.32, 126.26, 60.17, 31.86, 31.18, 22.17, 14.82, 13.89; EIMS *m/z* 429 (M^+, 16), 32 (21), 358 (61), 228 (86), 218 (49), 201 (100), 155 (19), 91 (19), 77 (29); HRMS (EI) *m/z* calcd for $C_{28}H_{32}NOP$ 429.2222, found 429.2238.



164

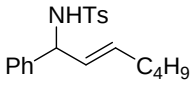
***N*-(3-Phenylprop-2-ynylidene)-*P*,*P*-diphenylphosphinamide (164).** A solution of 2.20 mL (20.0 mmol) of phenylacetylene in 50 mL of THF was cooled to -40 °C, treated with 12.5 mL (20.0 mmol) of *n*-BuLi (1.6 M solution in hexanes), stirred at -40 °C for 10 min, treated with 3.10 mL (40.0 mmol) of DMF, warmed to room temperature over 30 min, and stirred for 30 min. The mixture was quenched by pouring into a biphasic mixture of 10.0 g (73.4 mmol) of KH_2PO_4 in 90 mL of H_2O and 100 mL of MTBE at 0 °C.[236] The organic layer was separated, washed with H_2O, dried ($MgSO_4$), concentrated *in vacuo* and filtered through a pad of SiO_2 (9:1, hexanes/EtOAc). The residue (2.10 g, 81%) was used in the next step without further purification. According to the General Protocol B, 1.50 g (6.91 mmol) of *P*,*P*-diphenyl-phosphinamide, 1.35 g (10.4 mmol) of the crude aldehyde, 3.00 mL (21.5 mmol) of Et_3N, and 450 μL (4.10 mmol) of $TiCl_4$ afforded 914 mg (40%) of **164** as a yellow solid: mp 109-110 °C (CH_2Cl_2/hexanes); IR (KBr) 3056, 2199, 1585, 1439, 1214, 1124, 1109 cm^{-1}; ^1H NMR δ 8.72 (d, 1 H, J = 31.2 Hz), 7.90-7.86 (m, 4 H), 7.60-7.37 (m, 11 H); ^{13}C NMR δ 158.12, 132.88, 132.03, 131.68, 131.56, 131.06, 130.72, 128.60, 128.44, 120.45, 100.65, 88.38, 87.90; EIMS *m/z* 329 (M^+, 30), 216 (30), 201 (74), 130 (32), 102 (42), 77 (100); HRMS (EI) *m/z* calcd for $C_{21}H_{16}NOP$ 329.0970, found 329.0960.



165

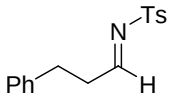
(*E*)-*N*-(1-Phenethynylhept-2-enyl)-*P*,*P*-diphenylphosphinamide (165). According to the General Protocol A, 195 mg (0.756 mmol) of Cp_2ZrHCl, 95.0 μL (0.827 mmol) of 1-hexyne, 380 μL (0.760 mmol) of Me_2Zn (2.0 M solution in toluene), and 165 mg (0.501 mmol) of imine **164** (2 h reaction time) afforded 176 mg (85%) of **165** as a colorless oil: IR (neat) 3144, 2957, 2928, 2853, 1592, 1490, 1438, 1190, 1124, 1110, 1058 cm^{-1}; ^1H NMR δ 8.09-8.02 (m, 2 H),

7.98-7.90 (m, 2 H), 7.56-7.37 (m, 9 H), 7.35-7.30 (m, 2 H), 5.95 (dtd, 1 H, *J* = 15.1, 6.8, 1.5 Hz), 5.71 (ddt, 1 H, *J* = 15.2, 5.2, 1.3 Hz), 4.75 (td, 1 H, *J* = 9.0, 5.2 Hz), 3.42 (dd, 1 H, *J* = 9.4, 7.5 Hz), 2.10-2.03 (m, 2 H), 1.40-1.29 (m, 4 H), 0.91 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 133.63, 132.96, 132.52, 132.40, 131.87, 131.75, 131.53, 131.17, 128.79, 128.41, 128.24, 128.07, 126.62, 122.75, 88.44, 84.86, 45.04, 31.40, 30.97, 22.10, 13.76; EIMS *m/z* 413 (M^+, 17), 370 (24), 356 (13), 216 (56), 212 (39), 201 (100), 196 (25), 167 (27), 154 (46), 124 (33), 115 (29), 91 (24), 77 (83); HRMS (EI) *m/z* calcd for $C_{27}H_{28}NOP$ 413.1909, found 413.1902.



91

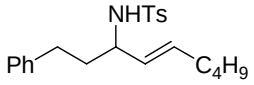
(*E*)-*N*-(1-Phenylhept-2-enyl)-*S*-(4-methylphenyl)sulfonamide (91). According to the General Protocol A, 195 mg (0.756 mmol) of Cp_2ZrHCl, 95.0 μL (0.827 mmol) of 1-hexyne, 380 μL (0.760 mmol) of Me_2Zn (2.0 M solution in toluene), and 130 mg (0.501 mmol) of imine **90** (4 h reaction time) afforded 138 mg (80%) of **91** as a colorless oil: IR (neat) 3272, 3030, 2956, 2927, 2858, 1454, 1433, 1328, 1161, 1094, 1043, 1027, 970, 932, 813, 749, 699, 668 cm^{-1}; ^{1}H NMR δ 7.65-7.61 (m, 2 H), 7.24-7.12 (m, 7 H), 5.48-5.34 (m, 2 H), 5.18 (d, 1 H, *J* = 7.4 Hz), 4.89 (dd, 1 H, *J* = 7.3, 5.2 Hz), 2.37 (s, 3 H), 1.90-1.84 (m, 2 H), 1.24-1.14 (m, 4 H), 0.83 (t, 3 H, *J* = 6.9 Hz); ^{13}C NMR δ 142.92, 140.27, 137.83, 133.72, 129.25, 128.64, 128.40, 127.37, 127.18, 126.90, 59.52, 31.66, 30.87, 22.11, 21.40, 13.83; EIMS *m/z* 343 (M^+, 4), 286 (40) 188 (90), 172 (29), 155 (44), 144 (21), 129 (32), 117 (46), 104 (39), 91 (100), 77 (21), 65 (30); HRMS (EI) *m/z* calcd for $C_{20}H_{25}NO_2S$ 343.1606, found 343.1607.



166

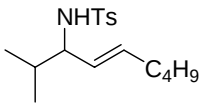
***N*-(3-Phenylpropylidene)-*S*-(4-methylphenyl)sulfonamide (166).** According to a literature procedure, a solution of 1.85 g (11.3 mmol) of sodium benzenesulfinate, 1.71 g (10.0 mmol) of $TsNH_2$, and 1.32 mL (10.0 mmol) of hydrocinnamaldehyde in 30 mL of 50% formic acid was stirred at room temperature for 16 h, diluted with 20 mL of H_2O, filtered and rinsed with H_2O and pentane. The filter cake was dissolved in 75 mL of CH_2Cl_2 and stirred with 75 mL of saturated $NaHCO_3$ for 2 h. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo*.

The residue was precipitated from CH_2Cl_2 with hexanes to yield 2.03 g (71%) of **166** as a colorless solid: mp 61-63 °C (CH_2Cl_2/hexanes); IR (KBr) 3271, 3030, 2938, 1634, 1613, 1494, 1453, 1318, 1159, 1091, 784, 705, 682 cm^{-1}; ^1H NMR δ 8.67 (t, 1 H, *J* = 4.0 Hz), 7.81 (d, 2 H, *J* = 8.3 Hz), 7.38-7.15 (m, 7 H), 3.02-2.96 (m, 2 H), 2.91-2.85 (m, 2 H), 2.49 (s, 3 H); ^{13}C NMR δ 177.36, 144.69, 139.53, 134.36, 129.75, 128.58, 128.25, 128.09, 126.41, 37.30, 30.53, 21.61; EIMS *m/z* 287 (M^+, 4), 171 (12), 155 (25), 132 (100), 105 (16), 91 (20); HRMS (EI) *m/z* calcd for $C_{16}H_{17}NO_2S$ 287.0980, found 287.0979.



167

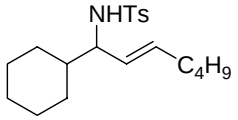
(*E*)-*N*-(1-Phenethylhept-2-enyl)-*S*-(4-methylphenyl)sulfonamide (167). According to the General Protocol A, 195 mg (0.756 mmol) of Cp_2ZrHCl, 95.0 μL (0.827 mmol) of 1-hexyne, 380 μL (0.760 mmol) of Me_2Zn (2.0 M solution in toluene), and 144 mg (0.501 mmol) of imine **166** (5 h reaction time) afforded 168 mg (90%) of **167** as a colorless oil: IR (neat) 3166, 3058, 2955, 2924, 2855, 1490, 1438, 1189, 1124, 1110, 1070, 755, 723, 692 cm^{-1}; ^1H NMR δ 7.73-7.69 (m, 2 H), 7.27-7.06 (m, 7 H), 5.30 (dtd, 1 H, *J* = 15.3, 6.7, 0.8 Hz), 5.07 (ddt, 1 H, *J* = 15.3, 7.4, 1.4 Hz), 4.84 (d, 1 H, *J* = 8.0 Hz), 3.73 (qn, 1 H, *J* = 7.2 Hz), 2.65-2.50 (m, 2 H), 2.39 (s, 3 H), 1.83-1.69 (m, 4 H), 1.20-1.10 (m, 4 H), 0.84 (t, 3 H, *J* = 6.9 Hz); ^{13}C NMR δ 142.97, 141.28, 138.18, 133.23, 129.39, 128.80, 128.34, 128.31, 127.19, 125.83, 55.77, 37.67, 31.69, 31.65, 30.94, 22.09, 21.43, 13.86; EIMS *m/z* 371 (M^+, 2), 314 (4), 288 (4), 267 (100), 216 (71), 200 (97), 155 (60), 143 (60), 139 (33), 117 (37), 105 (93); HRMS (EI) *m/z* calcd for $C_{22}H_{29}NO_2S$ 371.1919, found 371.1913.



169

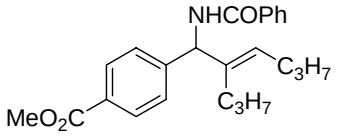
(*E*)-*N*-(1-Isopropylhept-2-enyl)-*S*-(4-methylphenyl)sulfonamide (169). According to the General Protocol A, 390 mg (1.51 mmol) of Cp_2ZrHCl, 190 μL (1.65 mmol) of 1-hexyne, 750 μL (1.50 mmol) of Me_2Zn (2.0 M solution in toluene), and 113 mg (0.502 mmol) of imine **168** (4 h reaction time) afforded 111 mg (72%) of **169** as a colorless oil: IR (neat) 3278, 2961, 2926, 2873, 1467, 1437, 1323, 1162, 1096, 1041, 972, 814, 667 cm^{-1}; ^1H NMR δ 7.75 (d, 2 H, *J* = 8.3 Hz), 7.27 (d, 2 H, *J* = 8.6 Hz), 5.21 (dt, 1 H, *J* = 15.6, 6.6), 5.05 (ddt, 1 H, *J* = 15.3, 7.6, 1.3

Hz), 4.98 (d, 1 H, *J* = 8.5 Hz), 3.53 (td, 1 H, *J* = 7.8, 5.7 Hz), 2.42 (s, 3 H), 1.81-1.67 (m, 3 H), 1.23-1.05 (m, 4 H), 0.87 (t, 6 H, *J* = 6.5 Hz), 0.85 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR δ 142.66, 138.32, 133.33, 129.19, 127.15, 126.87, 61.58, 32.99, 31.65, 30.94, 22.01, 21.34, 18.33, 18.14, 13.79; EIMS *m/z* 308 ([M-H]$^+$, 1), 266 (90), 226 (59), 155 (86), 139 (29), 111 (39), 91 (100); HRMS (EI) *m/z* calcd for $C_{17}H_{26}NO_2S$ [M-H] 308.1684, found 308.1687.



171

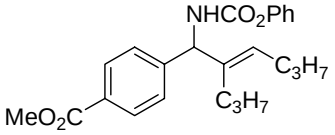
(*E*)-*N*-(1-Cyclohexylhept-2-enyl)-*S*-(4-methylphenyl)sulfonamide (171). According to the General Protocol A, 97.0 mg (0.376 mmol) of Cp_2ZrHCl, 50.0 μL (0.435 mmol) of 1-hexyne, 190 μL (0.380 mmol) of Me_2Zn (2.0 M solution in toluene), and 66.0 mg (0.249 mmol) of imine **170** (2 h reaction time) afforded 70 mg (81%) of **171** as a colorless solid: mp 102-103 °C (Et_2O/hexanes); IR (KBr) 3287, 2921, 2851, 1439, 1326, 1151, 1090, 1044 cm^{-1}; ^{1}H NMR δ 7.70-7.67 (m, 2 H), 7.24-7.21 (m, 2 H), 5.13 (dt, 1 H, *J* = 15.3, 6.4 Hz), 4.99 (ddt, 1 H, *J* = 15.3, 7.6, 1.2 Hz), 4.63 (d, 1 H, *J* = 8.5 Hz), 3.49 (td, 1 H, *J* = 8.0, 6.1 Hz), 2.38 (s, 3 H), 1.77-1.56 (m, 7 H), 1.37-1.26 (m, 1 H), 1.21-1.01 (m, 7 H), 0.99-0.86 (m, 2 H), 0.81 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR δ 142.78, 138.43, 133.32, 129.28, 127.28, 127.22, 61.10, 42.83, 31.73, 31.03, 28.92, 28.83, 26.28, 25.99, 22.12, 21.43, 13.87; EIMS *m/z* 349 (M$^+$, 1), 266 (100), 155 (48), 91 (84); HRMS (EI) *m/z* calcd for $C_{20}H_{31}NO_2S$ 349.2076, found 349.2074.



173

(*E*)-Methyl 4-(1-benzoylamino-2-propylhex-2-enyl)benzoate (173). A solution of 48.0 mg (0.101 mmol) of phosphinamide **172** in 5.7 mL of a 2 N solution of HCl(g) in MeOH (prepared by treating 5 mL of MeOH with 0.7 mL of acetyl chloride at 0 °C and stirring at room temperature for 30 min) was stirred at room temperature for 12 h, concentrated *in vacuo*, dissolved in 5 mL of CH_2Cl_2, and concentrated *in vacuo*. A solution of the residue in 1 mL of CH_2Cl_2 was treated with 27.0 μL (0.233 mmol) of PhCOCl, 60.0 μL (0.344 mmol) of (*i*-Pr)$_2$NEt, and 2.0 mg (0.016 mmol) of DMAP. The mixture was stirred at room temperature for 1 h, concentrated to ~0.5 mL by rotary evaporation, and chromatographed on SiO_2 (80:20, hexanes/

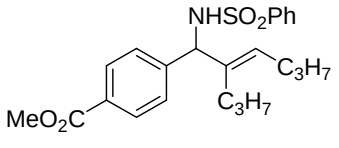
EtOAc) to afford 32 mg (84%) of **173** as a colorless oil: IR (thin film) 3571, 3311, 2959, 2869, 1725, 1637, 1525, 1277, 1107 cm^{-1}; ^1H NMR δ 8.01 (d, 2 H, *J* = 8.4 Hz), 7.80 (d, 2 H, *J* = 8.4 Hz), 7.55-7.38 (m, 5 H), 6.42 (d, 1 H, *J* = 8.0 Hz), 5.81 (d, 1 H, *J* = 8.1 Hz), 5.33 (t, 1 H, *J* = 7.1 Hz), 3.91 (s, 3 H), 2.18-1.92 (m, 4 H), 1.53-1.31 (m, 4 H), 0.92 (t, 3 H, *J* = 7.3 Hz), 0.89 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR δ 166.83, 166.40, 146.27, 138.81, 134.38, 131.63, 129.84 (2 C), 129.26, 129.10, 128.65 (2 C), 127.34 (2 C), 126.93 (2 C), 57.84, 52.02, 31.77, 29.82, 22.82, 22.14, 14.20, 13.83; EIMS *m*/*z* 379 (M^+, 46), 336 (59), 322 (56), 105 (100), 77 (48); HRMS (EI) *m*/*z* calc'd for $C_{24}H_{29}NO_3$ 379.2147, found 379.2143.



174

(*E*)-Methyl 4-(1-phenoxycarbonylamino-2-propylhex-2-enyl)benzoate (174).

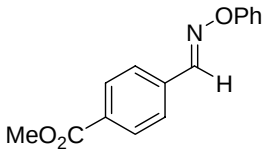
A solution of 44.0 mg (0.0925 mmol) of phosphinamide **172** in 5.7 mL of a 2 N solution of HCl(g) in MeOH (prepared by treating 5 mL of MeOH with 0.7 mL of acetyl chloride at 0 °C and stirring at room temperature for 30 min) was stirred at room temperature for 12 h, concentrated *in vacuo*, dissolved in 5 mL of CH_2Cl_2, and concentrated *in vacuo*. A solution of the residue in 1 mL of CH_2Cl_2 was treated with 55.0 μL (0.316 mmol) of $(i\text{-Pr})_2NEt$, 26.0 μL (0.207 mmol) of $ClCO_2Ph$, and 2.0 mg (0.016 mmol) of DMAP. The mixture was stirred at room temperature for 1 h, concentrated to ~0.5 mL by rotary evaporation, and chromatographed on SiO_2 (80:20, hexanes/EtOAc) to afford 33 mg (90%) of **174** as a colorless oil: IR (thin film) 3336, 2957, 2869, 1723, 1524, 1490, 1281, 1207, 1112, 1018 cm^{-1}; ^1H NMR δ 8.03 (d, 2 H, *J* = 8.3 Hz), 7.46-7.12 (m, 7 H), 5.40-5.36 (m, 3 H), 3.93 (s, 3 H), 2.14-2.04 (m, 3 H), 1.96-1.86 (m, 1 H), 1.46-1.34 (m, 4 H), 0.92 (t, 3 H, *J* = 7.3 Hz), 0.91 (t, 3 H, *J* = 7.3 Hz); ^{13}C NMR δ 166.77, 150.96, 145.99, 138.44, 129.85 (2 C), 129.51, 129.38, 129.22 (2 C), 127.20 (2 C), 125.31, 121.45 (2 C), 120.86, 52.03, 31.43, 29.75, 22.78, 22.05, 14.14, 13.80; EIMS *m*/*z* 395 (M^+, 2), 364 (8), 301 (23), 259 (100), 227 (22), 214 (45), 170 (24), 141 (34), 128 (34), 94 (95), 77 (63); HRMS (EI) *m*/*z* calc'd for $C_{24}H_{29}NO_4$ 395.2097, found 395.2101.



175

(*E*)-Methyl 4-(1-Benzenesulfonylamino-2-propylhex-2-enyl)benzoate (175).

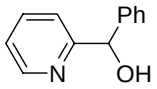
A solution of 43.0 mg (0.0904 mmol) of phosphinamide **172** in 5.7 mL of a 2 N solution of HCl(g) in MeOH (prepared by treating 5 mL of MeOH with 0.7 mL of acetyl chloride at 0 °C and stirring at room temperature for 30 min) was stirred at room temperature for 12 h, concentrated *in vacuo*, dissolved in 5 mL of CH_2Cl_2, and concentrated *in vacuo*. A solution of the residue in 1 mL of CH_2Cl_2 was treated with 53.0 μL (0.304 mmol) of $(i\text{-Pr})_2NEt$, 26.0 μL (0.204 mmol) of $PhSO_2Cl$, and 2.0 mg (0.016 mmol) of DMAP. The mixture was stirred at room temperature for 1 h, concentrated to ~0.5 mL by rotary evaporation, and chromatographed on SiO_2 (80:20, hexanes/EtOAc) to afford 29 mg (77%) of **175** as a colorless oil: IR (thin film) 3285, 2957, 2873, 1723, 1447, 1442, 1329, 1280, 1163, 1110 cm^{-1}; ^1H NMR δ 7.85 (d, 2 H, J = 8.4 Hz), 7.74 (d, 2 H, J = 8.1 Hz), 7.52-7.46 (m, 1 H), 7.41-7.35 (m, 2 H), 7.17 (d, 2 H, J = 8.3 Hz), 5.19-5.12 (m, 2 H), 4.96 (d, 1 H, J = 7.7 Hz), 3.90 (s, 3 H), 1.92-1.70 (m, 4 H), 1.30-1.12 (m, 4 H), 0.81 (t, 3 H, J = 7.3 Hz), 0.77 (t, 3 H, J = 7.3 Hz); ^{13}C NMR δ 166.70, 144.98, 140.53, 137.74, 132.42, 130.08, 129.57 (2 C), 129.24, 128.76 (2 C), 127.25 (2 C), 127.09 (2 C), 61.76, 52.02, 30.88, 29.70, 22.54, 21.94, 14.06, 13.75; EIMS m/z 415 (M^+, 1), 384 (1), 372 (1), 340 (1), 304 (16), 274 (19), 258 (17), 141 (31), 132 (20), 77 (100); HRMS (EI) m/z calc'd for $C_{23}H_{29}NO_4S$ 415.1817, found 415.1819.



180

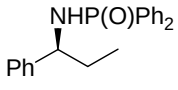
Methyl 4-(phenoxyiminomethyl)benzoate (180). According to a literature procedure,[237] a solution of 400 mg (2.75 mmol) of *O*-phenylhydroxylamine hydrochloride and 361 mg (2.20 mmol) of methyl 4-formylbenzoate in 10 mL of pyridine was stirred at room temperature for 12 h, and concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with saturated $CuSO_4$, H_2O and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (4:1, hexanes/EtOAc) to yield 533 mg (95%) of **180** as a pale

yellow solid: mp 61-63 °C (EtOAc/hexane); IR (thin film) 1720, 1591, 1489, 1435, 1285, 1215, 1115, 935, 768, 746, 698, 687 cm^{-1}; ^1H NMR δ 8.45 (s, 1 H), 8.11 (dt, 2 H, *J* = 8.3, 1.7 Hz), 7.80 (dt, 2 H, *J* = 8.2, 1.6 Hz), 7.40-7.34 (m, 2 H), 7.28 (d, 2 H, *J* = 7.9 Hz), 7.08 (t, 1 H, *J* = 7.2 Hz), 3.96 (s, 3 H); ^{13}C NMR δ 166.44, 159.20, 150.50, 135.65, 131.72, 130.02 (2 C), 129.38 (2 C), 127.44 (2 C), 122.67, 114.57 (2 C), 52.32; EIMS *m/z* 255 (M^+, 19), 162 (25), 130 (38), 94 (100); HRMS (EI) *m/z* calcd for $C_{15}H_{13}NO_3$ 255.0895, found 255.0893.



189

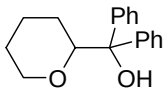
Phenyl(pyridin-2-yl)methanol (189).[238] A solution of 890 μL (9.36 mmol) of 2-pyridinecarboxaldehyde in 20 mL of THF was cooled to 0 °C and treated dropwise with a solution of 3.70 mL (11.1 mmol) of PhMgBr (3.0 M solution in Et_2O) in 20 mL of THF. The mixture was stirred at 0 °C for 3 h, quenched with saturated NH_4Cl and extracted with 1N HCl (2x). The aqueous extracts were basified with K_2CO_3 to pH 8, extracted with Et_2O (2x), washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford 1.21 g (70%) of **189** as a colorless solid: ^1H NMR δ 8.57 (s, 1 H), 7.62 (t, 1 H, *J* = 7.6 Hz), 7.41-7.27 (m, 5 H), 7.22-7.15 (m, 2 H), 5.77 (s, 1 H), 5.16 (bs, 1 H). Approximately 600 mg of racemic **189** was separated by HPLC on a Chiracel AD semi-preparative column (solvent system: 15% *i*-PrOH in hexanes; flow rate: 10 mL/min). (*R*)-Enantiomer: R_t 16.0 min; 99.9% *ee* (HPLC chiracel AD analytical column, 15% *i*-PrOH in hexanes, 1.0 mL/min); α_D -156 ($CHCl_3$, c = 1.00), lit.[239] -163 ($CHCl_3$, c = 0.4). (*S*)-Enantiomer: R_t 19.5 min; 99.9% *ee* (HPLC chiracel AD analytical column, 15% *i*-PrOH in hexanes, 1.0 mL/min); α_D +158 ($CHCl_3$, c = 1.00), lit. +163 ($CHCl_3$, c = 0.4).



(*S*)-**106**

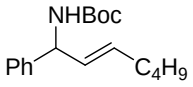
(*S*)-*N*-(1-Phenylpropyl)-*P,P*-diphenylphosphinamide (106).[162] A solution of 75.0 mg (0.246 mmol) of imine **104**, 46.0 mg (0.248 mmol) of (*S*)-**189**, and 670 μL (0.737 mmol) of Et_2Zn (1.1 M solution in toluene) in 1 mL of toluene was stirred at room temperature for 48 h. The mixture was quenched with saturated NH_4Cl, extracted with CH_2Cl_2 (2x), washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative TLC (EtOAc) to yield 61 mg (74%) of (*S*)-**106** as a colorless solid: ^1H NMR δ 7.87 (ddt, 2 H, *J* =

11.9, 6.6, 1.6 Hz), 7.76 (ddt, 2 H, *J* = 12.1, 6.9, 1.5 Hz), 7.52-7.38 (m, 4 H), 7.35-7.20 (m, 5 H), 7.16 (dt, 2 H, *J* = 6.5, 1.6 Hz), 4.16-4.05 (m, 1 H), 3.27 (t, 1 H, *J* = 7.5 Hz), 2.09-1.95 (m, 1 H), 1.91-1.77 (m, 1 H), 0.79 (t, 3 H, *J* = 7.4 Hz). The enantioselectivity was measured by chiral HPLC using a Chiracel OD column (15% *i*-PrOH in hexanes, 1.0 mL/min, R_T = 5.7 and 6.9 min): 93% *ee*.



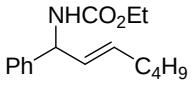
190

(Tetrahydro-2*H*-pyran-2-yl)diphenylmethanol (190). A suspension of 1.23 g (50.6 mmol) of Mg in 40 mL of THF was cooled to 0 °C and treated with 5.30 mL (50.3 mmol) of bromobenzene. The mixture was stirred at room temperature for 30 min, heated at reflux for 1 h, cooled to 0 °C, treated dropwise with a solution of 2.00 g (12.6 mmol) of ethyl tetrahydro-2*H*-pyran-2-carboxylate[240] in 10 mL of THF, slowly warmed to room temperature over 16 h, quenched with cold saturated NH_4Cl then 1 N HCl, and extracted with Et_2O (3x). The combined extracts were washed with H_2O and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (9:1, hexanes/EtOAc) to yield 2.34 g (69%) of **190** as a pale yellow solid: mp 95-96 °C (Et_2O/hexane); IR (thin film) 3479, 2935, 2856, 1492, 1448, 1330, 1172, 1090, 1048, 873, 748, 697 cm^{-1}; ^1H NMR δ 7.57-7.53 (m, 2 H), 7.42-7.16 (m, 8 H), 4.24 (dd, 1 H, *J* = 10.7, 1.9 Hz), 4.10-4.04 (m, 1 H), 3.62 (td, 1 H, *J* = 11.0, 3.5 Hz), 3.24 (s, 1 H), 1.88-1.83 (m, 1 H), 1.67-1.39 (m, 4 H), 1.14-1.09 (m, 1 H); ^{13}C NMR δ 146.52, 143.86, 127.94 (2 C), 127.90 (2 C), 126.83 (2 C), 126.68, 126.47, 125.80 (2 C), 80.19, 79.19, 68.75, 25.83, 24.89, 23.31; EIMS *m/z* 250 ($[M-H_2O]^+$, 11), 206 (18), 183 (35), 160 (32), 131 (59), 124 (100), 105 (42), 91 (43), 77(52); HRMS (EI) *m/z* calcd for $C_{18}H_{20}O_2$ [M-H_2O] 250.1358, found 250.1360. Approximately 500 mg of racemic **190** was separated by HPLC on a Chiracel AD semi-preparative column (solvent system: 1.2% *i*-PrOH in hexanes; flow rate: 10 mL/min). Enantiomer 1: R_t 19.5 min; 93.4% *ee* (HPLC chiracel AD analytical column, 1.2% *i*-PrOH in hexanes, 1.0 mL/min); α_D +170 ($CHCl_3$, c = 0.88). Enantiomer 2: R_t 22.0 min; 86.7% *ee* (HPLC chiracel AD analytical column, 1.2% *i*-PrOH in hexanes, 1.0 mL/min); α_D -146 ($CHCl_3$, c = 0.14).



196

(*E*)-*O*-*tert*-Butyl-*N*-(1-phenylhept-2-enyl)carbamate (196). A suspension of 95.0 mg (0.368 mmol) of Cp_2ZrHCl in 1 mL of CH_2Cl_2 was treated with 50.0 μL (0.435 mmol) of 1-hexyne, stirred at room temperature for 5 min, and concentrated *in vacuo*. A solution of the residue in 1 mL of toluene was treated with 5.3 mg (0.027 mmol) of amino thiol **56**, cooled to -50 °C, and treated with 190 μL (0.380 mmol) of Me_2Zn (2.0 M solution in toluene). The mixture was slowly warmed from -50 °C to -30 °C over 1 h, treated with a solution of 51.0 mg (0.248 mmol) of imine **176** in 1 mL of toluene, stirred at -30 °C for 12 h, quenched with saturated $NaHCO_3$, diluted with Et_2O, filtered through Celite, washed with H_2O and brine, dried ($MgSO_4$), filtered through Florisil, and concentrated *in vacuo*. The residue was chromato-graphed on SiO_2 (9:1, hexanes/EtOAc) to yield 58 mg (81%) of **196** as a colorless solid: mp 39-40 °C (EtOAc/hexanes); IR (thin film) 3332, 2961, 2927, 1699, 1495, 1366, 1248, 1171, 700 cm^{-1}; ^1H NMR δ 7.34-7.20 (m, 5 H), 5.66-5.50 (m, 2 H), 5.21 (bs, 1 H), 4.89 (bs, 1 H), 2.04 (q, 2 H, J = 6.4 Hz), 1.42 (s, 9 H), 1.37-1.20 (m, 4 H), 0.87 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 154.97, 142.04, 132.45, 129.73, 128.43, 127.10, 126.73, 79.42, 56.10, 31.83, 31.21 28.31, 22.13, 13.84; EIMS *m/z* 289 (M^+, 1), 233 (56), 176 (100), 132 (86); HRMS (EI) *m/z* calcd for $C_{18}H_{27}NO_2$ 289.2042, found 289.2047. The enantioselectivity was measured by chiral HPLC using a Chiracel OD column (0.1% *i*-PrOH in hexanes, 1.0 mL/min, R_T = 13.1 and 14.3 min): 22% *ee*.

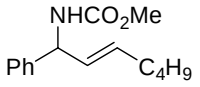


198

(*E*)-*O*-Ethyl-*N*-(1-phenylhept-2-enyl)carbamate (198). A suspension of 220 mg (0.853 mmol) of Cp_2ZrHCl in 2 mL of CH_2Cl_2 was treated with 115 μL (1.00 mmol) of 1-hexyne, stirred at room temperature for 10 min, and concentrated *in vacuo*. A solution of the residue in 1 mL of toluene was cannulated into a cold (-30 °C) solution of 10.2 mg (0.0563 mmol) of amino thiol **181**, and 420 μL (0.840 mmol) of Me_2Zn (2.0 M solution in toluene) in 1 mL of toluene. The mixture was stirred at -30 °C for 30 min, treated with a solution of 100 mg (0.564 mmol) of imine **197** in 1 mL of toluene, stirred at -30 °C for 12 h, quenched with saturated NH_4Cl, diluted with EtOAc, washed with 1 N HCl and brine, dried ($MgSO_4$), filtered through Florisil, and

concentrated *in vacuo*. The residue was chromatographed on SiO_2 (4:1, hexanes/EtOAc) to yield 138 mg (94%) of **198** as a colorless oil: IR (thin film) 3324, 2959, 2925, 1698, 1528, 1245, 1074, 1040, 969, 699 cm^{-1}; ^1H NMR δ 7.38-7.24 (m, 5 H), 5.70-5.54 (m, 2 H), 5.28 (bs, 1 H), 5.00 (bs, 1 H), 4.13 (q, 2 H, *J* = 7.1 Hz), 2.07 (q, 2 H, *J* = 6.5 Hz), 1.42-1.29 (m, 4 H), 1.24 (t, 3 H, *J* = 7.1 Hz), 0.90 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 155.75, 141.76, 132.76, 129.44, 128.55 (2 C), 127.31, 126.79 (2 C), 60.90, 56.42, 31.88, 31.21, 22.19, 14.56, 13.90; ESIMS *m/z* 300 ($[M+K]^+$, 100), 284 ($[M+Na]^+$, 78); HRMS (ESI) *m/z* calcd for $C_{16}H_{23}NO_2Na$ [M+Na] 284.1626, found 284.1640. The enantioselectivity was measured by chiral HPLC using a Chiracel OD column (3.5% *i*-PrOH in hexanes, 1.0 mL/min, R_T = 7.2 and 12.6 min): 7% *ee*.

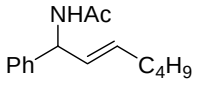
Preparation of 198 using a modified General Protocol A (*in situ* imine formation). A suspension of 161 mg (0.624 mmol) of Cp_2ZrHCl in 2 mL of CH_2Cl_2 was treated with 80.0 μL (0.696 mmol) of 1-hexyne, stirred at room temperature for 10 min, and concentrated *in vacuo*. A solution of the residue in 1 mL of toluene was cannulated into a cold (-20 °C) solution of 100 mg (0.313 mmol) of sulfonamide **204**,[241] 8.4 mg (0.031 mmol) of amino alcohol **55**, and 240 μL (0.420 mmol) of Me_2Zn (2.0 M solution in toluene) in 2 mL of toluene. The mixture was stirred at -20 °C for 6 h, quenched with saturated NH_4Cl, diluted with EtOAc, washed with 1 N HCl and brine, dried ($MgSO_4$), diluted in hexanes, filtered through Florisil, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (4:1, hexanes/EtOAc) to yield 42 mg (51%) of **198** as a colorless oil. The enantioselectivity was measured by chiral HPLC using a Chiracel OD column (3.5% *i*-PrOH in hexanes, 1.0 mL/min, R_T = 5.6, 12.6 min): 5% *ee*.



200

(*E*)-*O*-Methyl-*N*-(1-phenylhept-2-enyl)carbamate (200). A suspension of 127 mg (0.492 mmol) of Cp_2ZrHCl in 1 mL of THF was treated with 60.0 μL (0.522 mmol) of 1-hexyne, stirred at room temperature for 15 min, and concentrated *in vacuo*. A solution of the residue in 1 mL of toluene was cannulated into a cold (-40 °C) solution of 27.0 mg (0.165 mmol) of imine **199**, 44.0 mg (0.163 mmol) of amino alcohol **55**, and 250 μL (0.500 mmol) of Me_2Zn (2.0 M solution in toluene) in 1 mL of toluene. The mixture was stirred at -20 °C for 12 h, quenched with saturated NH_4Cl, diluted with EtOAc, washed with 1 N HCl and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (4:1, hexanes/EtOAc) to yield

35 mg (86%) of **200** as a colorless oil: IR (thin film) 3324, 2959, 2929, 1707, 1527, 1453, 1248, 1069, 1021, 970, 774, 699 cm^{-1}; ^1H NMR δ7.37-7.24 (m, 5 H), 5.68-5.54 (m, 2 H), 5.29 (bs, 1 H), 5.07 (bs, 1 H), 3.68 (s, 3 H), 2.07 (q, 2 H, *J* = 6.4 Hz), 1.42-1.28 (m, 4 H), 0.90 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR δ 156.13, 141.72, 132.82, 129.46, 128.53 (2 C), 127.30, 126.74 (2 C), 56.64, 52.08, 31.82, 31.20, 22.14, 13.80; EIMS *m/z* 247 (M^+, 13), 190 (74), 147 (42), 143 (50), 129 (84), 115 (65), 105 (100), 91 (34), 77 (58); HRMS (EI) *m/z* calcd for $C_{15}H_{21}NO_2$ 247.1572, found 247.1578. The enantioselectivity was measured by chiral HPLC using a Chiracel OD column (5% *i*-PrOH in hexanes, 1.0 mL/min, R_T = 8.5, 15.0 min): 6% *ee*.

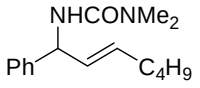


201

(*E*)-*N*-(1-Phenylhept-2-enyl)acetamide (201). A suspension of 100 mg (0.388 mmol) of Cp_2ZrHCl in 2 mL of CH_2Cl_2 was treated with 50.0 μL (0.435 mmol) of 1-hexyne, stirred at room temperature for 10 min, and concentrated *in vacuo*. A solution of the residue in 1.5 mL of toluene was cooled to -30 °C, and treated with 5.0 mg (0.028 mmol) of amino thiol **181** and 200 μL (0.400 mmol) of Me_2Zn (2.0 M solution in toluene). The mixture was stirred for 30 min at -30 °C, treated with a solution of 42.0 mg (0.285 mmol) of imine **177** in 0.5 mL of toluene, stirred at -30 °C for 12 h, quenched with saturated NH_4Cl, diluted with EtOAc, washed with 1 N HCl and brine, dried ($MgSO_4$), filtered through Florisil, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (1:1, hexanes/EtOAc) to yield 29 mg (44%) of **201** as a colorless oil: IR (thin film) 3279, 2957, 2927, 1652, 1538, 1372, 1292, 970, 698 cm^{-1}; ^1H NMR δ 7.37-7.23 (m, 5 H), 5.95 (bd, 1 H, *J* = 7.1 Hz), 5.64-5.55 (m, 3 H), 2.06 (q, 2 H, *J* = 7.0 Hz), 2.01 (s, 3 H), 1.41-1.25 (m, 4 H), 0.89 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 168.92, 141.44, 132.86, 128.91, 128.55 (2 C), 127.33, 126.98 (2 C), 54.59, 31.88, 31.19, 23.37, 22.20, 13.88; ESIMS *m/z* 270 ($[M+K]^+$, 28), 254 ($[M+Na]^+$, 100); HRMS (ESI) *m/z* calcd for $C_{15}H_{21}NONa$ [M+Na] 254.1521, found 254.1527. The enantioselectivity was measured by chiral HPLC using a Chiracel OD column (10% *i*-PrOH in hexanes, 1.0 mL/min, R_T = 6.8 and 7.8 min): 1% *ee*.

Preparation of 200 using a modified General Protocol A (*in situ* imine formation). A suspension of 161 mg (0.624 mmol) of Cp_2ZrHCl in 2 mL of CH_2Cl_2 was treated with 80.0 μL (0.696 mmol) of 1-hexyne, stirred at room temperature for 10 min, and concentrated *in vacuo*. A solution of the residue in 1 mL of toluene was cannulated into a cold (-20 °C) solution of 91.0

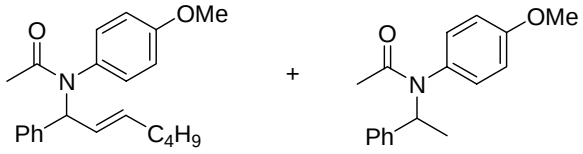
mg (0.314 mmol) of sulfonamide **205**,[242] 8.4 mg (0.0312 mmol) of amino alcohol **55**, and 240 μL (0.420 mmol) of Me_2Zn (2.0 M solution in toluene) in 2 mL of toluene. The mixture was stirred at -20 °C for 12 h, quenched with saturated NH_4Cl, diluted with EtOAc, washed with 1 N HCl and brine, dried ($MgSO_4$), filtered through Florisil, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (1:1, hexanes/EtOAc) to yield 35 mg (48%) of **201** as a colorless oil. The enantioselectivity was measured by chiral HPLC using a Chiracel OD column (1.0 mL/min, 10% *i*-PrOH in hexanes, R_T = 6.4 and 8.0 min): 6% *ee*.



203

(*E*)-1,1-Dimethyl-3-(1-phenylhept-2-enyl)urea (203). A solution of 3.00 g (34.0 mmol) of 1,1-dimethylurea, 5.0 mg (0.026 mmol) of $TsOH \cdot H_2O$, and 3.50 mL (34.4 mmol) of PhCHO in 50 mL of toluene was heated at reflux with a Dean-Stark trap for 16 h, and concentrated *in vacuo*. The residue was purified by Kugelrohr distillation (80 °C, ~1 atm) to afford 4.49 g (75%) of a pale yellow oil which was an 86:14 mixture of imine **202** to 1,1-dimethylurea. This mixture was used without further purification in the subsequent reaction. A suspension of 110 mg (0.427 mmol) of Cp_2ZrHCl in 2 mL of CH_2Cl_2 was treated with 55.0 μL (0.479 mmol) of 1-hexyne, stirred at room temperature for 5 min, and concentrated *in vacuo*. A solution of the residue in 2 mL of toluene was cooled to -30 °C, and treated with 5.1 mg (0.028 mmol) of amino thiol **181** and 210 μL (0.420 mmol) of Me_2Zn (2.0 M solution in toluene). The mixture was stirred for 30 min at -30 °C, treated with a solution of 50.0 mg (0.244 mmol) of imine **202** (86% purity) in 0.5 mL of toluene, stirred at -30 °C for 12 h, quenched with saturated NH_4Cl, diluted with EtOAc, washed with 1 N HCl and brine, dried ($MgSO_4$), filtered through Florisil, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (3:2, hexanes/EtOAc) to yield 44 mg (69%) of **203** as a colorless solid: mp 65-66 °C (EtOAc/hexanes); IR (thin film) 3330, 2925, 1631, 1527, 1376, 1214, 969, 698 cm^{-1}; ^1H NMR δ 7.36-7.23 (m, 5 H), 5.66-5.59 (m, 2 H), 5.49 (bd, 1 H, *J* = 5.5 Hz), 4.63 (bd, 1 H, *J* = 7.3 Hz), 2.93 (s, 6 H), 2.10-2.03 (m, 2 H), 1.42-1.28 (m, 4 H), 0.89 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR δ 157.46, 142.90, 132.38, 130.47, 128.46 (2 C), 127.01, 126.95 (2 C), 55.95, 36.19 (2 C), 31.92, 31.31, 22.22, 13.83; EIMS *m/z* 260 (M^+, 7), 172 (33), 143 (59), 129 (100), 115 (37), 91 (30); HRMS (EI) *m/z* calcd for $C_{16}H_{24}N_2O$ 260.1889, found

260.1888. The enantioselectivity was measured by chiral HPLC using a Chiracel OD column (5% *i*-PrOH in hexanes, 1.0 mL/min, R_T = 13.4 and 15.0 min): 6% *ee*.



207 **208**

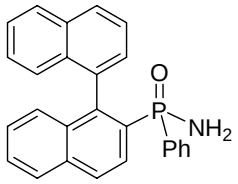
(*E*)-*N*-(4-Methoxyphenyl)-*N*-(1-phenylhept-2-enyl)acetamide (207) and *N*-(4-methoxyphenyl)-*N*-(1-phenylethyl)acetamide (208). A solution of 100 mg (0.473 mmol) of imine **178** in 2 mL of toluene was cooled to 0 °C, treated with 35.0 μL (0.492 mmol) of AcCl, warmed to room temperature and stirred for 1 h. Separately, a suspension of 183 mg (0.710 mmol) of Cp_2ZrHCl in 2 mL of CH_2Cl_2 was treated with 90.0 μL (0.783 mmol) of 1-hexyne, stirred at room temperature for 15 min, concentrated *in vacuo*, and dissolved in 2 mL of toluene. The two solutions were combined at room temperature, cooled to 0 °C, and treated with 240 μL (0.480 mmol) of Me_2Zn (2.0 M solution in toluene). The mixture was warmed to room temperature, stirred for 12 h, quenched with saturated NH_4Cl, diluted with EtOAc, washed with 1 N HCl and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (2:1, hexanes/EtOAc) to yield 82 mg (51%) of **207** and 41 mg (32%) of **208** as brown oils. **207**: IR (thin film) 2957, 2927, 2858, 1658, 1511, 1383, 1295, 1250, 1033, 975, 837, 733, 701 cm^{-1}; ^1H NMR δ 7.31-7.13 (m, 5 H), 6.76 (bs, 4 H), 6.50 (d, 1 H, *J* = 8.7 Hz), 5.83 (dt, 1 H, *J* = 15.2, 6.6 Hz), 5.56 (dd, 1 H, *J* = 15.3, 8.7 Hz), 3.77 (s, 3 H), 2.06 (q, 2 H, *J* = 6.6 Hz), 1.79 (s, 3 H), 1.44-1.24 (m, 4 H), 0.88 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 170.25, 158.96, 140.62, 135.50, 132.71, 131.12 (2 C), 128.15 (2 C), 127.96 (2 C), 127.03, 126.57, 113.88 (2 C), 59.96, 55.21, 31.98, 31.05, 23.02, 22.06, 13.73; ESIMS *m/z* 360 ($[M+Na]^+$, 100), 338 ($[M+H]^+$, 13); HRMS (ESI) *m/z* calcd for $C_{22}H_{27}NO_2Na$ [M+Na] 360.1939, found 360.1931. **208**: IR (thin film) 2974, 2937, 1653, 1510, 1454, 1387, 1315, 1292, 1248, 1032, 835, 700 cm^{-1}; ^1H NMR δ 7.29-7.17 (m, 5 H), 6.76 (bs, 4 H), 6.29 (q, 1 H, *J* = 7.2 Hz), 3.78 (s, 3 H), 1.77 (s, 3 H), 1.40 (d, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ 170.53, 159.08, 141.25, 131.65, 131.26 (2 C), 128.10 (2 C), 128.01 (2 C), 127.31, 113.93 (2 C), 55.29, 51.73, 23.25, 17.07; ESIMS *m/z* 292 ($[M+Na]^+$, 100), 270 ($[M+H]^+$, 18); HRMS (ESI) *m/z* calcd for $C_{17}H_{19}NO_2Na$ [M+Na] 292.1313, found 292.1313.

Preparation of 207 using catalytic $ZnCl_2$. A solution of 100 mg (0.473 mmol) of imine **178** in 2 mL of toluene was cooled to 0 °C, treated with 35.0 μL (0.492 mmol) of AcCl, warmed

to room temperature and stirred for 15 min. Separately, a suspension of 185 mg (0.717 mmol) of Cp_2ZrHCl in 2 mL of CH_2Cl_2 was treated with 90.0 μL (0.783 mmol) of 1-hexyne and stirred at room temperature for 10 min. The two solutions were combined at room temperature, cooled to 0 °C, and treated with 10.0 μL (0.0100 mmol) of $ZnCl_2$ (1.0 M solution in Et_2O). The mixture was stirred at 0 °C for 10 min, quenched with saturated NH_4Cl, diluted with EtOAc, washed with 1 N HCl and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (2:1, hexanes/EtOAc) to yield 131 mg (82%) of **207** as a brown oil.

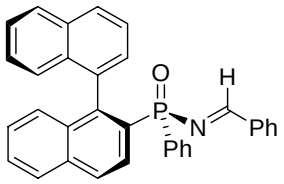
Preparation of 207 using catalytic CuBr. A solution of 100 mg (0.473 mmol) of imine **178** in 2 mL of toluene was cooled to 0 °C, treated with 35.0 μL (0.492 mmol) of AcCl, warmed to room temperature and stirred for 15 min. Separately, a suspension of 185 mg (0.717 mmol) of Cp_2ZrHCl in 2 mL of CH_2Cl_2 was treated with 90.0 μL (0.783 mmol) of 1-hexyne and stirred at room temperature for 10 min. The two solutions were combined at room temperature, cooled to 0 °C, and treated with 5.0 mg (0.035 mmol) of CuBr. The mixture was stirred at 0 °C for 30 min, quenched with saturated NH_4Cl, diluted with EtOAc, washed with 1 N HCl and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (2:1, hexanes/ EtOAc) to yield 137 mg (86%) of **207** as a brown oil.

Representative attempted asymmetric preparation of 207 using Cu catalysis. A suspension of 50.0 mg (0.237 mmol) of imine **178**, 1.9 mg (0.019 mmol) of CuCl, and 12.0 mg (0.0241 mmol) of (*R*,*R*)-DIOP (**215**) in 1 mL of toluene was cooled to 0 °C, treated with 17.0 μL (0.239 mmol) of AcCl, warmed to room temperature and stirred for 15 min. Separately, a suspension of 90.0 mg (0.349 mmol) of Cp_2ZrHCl in 1 mL of CH_2Cl_2 was treated with 45.0 μL (0.392 mmol) of 1-hexyne and stirred at room temperature for 10 min. The two solutions were combined at room temperature, stirred for 12 h, quenched with with 1 N HCl, extracted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (2:1, hexanes/EtOAc) to yield 57 mg (71%) of **207** as a brown oil. The enantioselectivity was measured by chiral HPLC using a Chiracel AD column (5% *i*-PrOH in hexanes, 1.0 mL/min, R_T = 13.6 and 15.3 min): 3% *ee*.



218

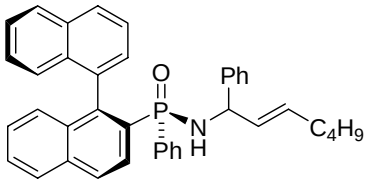
***P*-2-(1,1'-Binaphthyl)-*P*-phenylphosphinamide (218).** A mixture of 1.34 g (3.56 mmol) of phosphole oxide **240** and 500 mg (12.5 mmol) of crushed NaOH was slowly heated at 280 °C over 3 h. The mixture was stirred at 280 °C for 2 h, cooled to room temperature, and partitioned between CH_2Cl_2 and 2 N NaOH. The aqueous layer was separated, cooled to 0 °C, acidified to pH 4 with conc. HCl, and filtered. The filter cake was dissolved in CH_2Cl_2, dried ($MgSO_4$), and concentrated *in vacuo*. A solution of the residue in 20 mL of CH_2Cl_2 was cooled to 0 °C, treated with 600 μL (6.88 mmol) of $(COCl)_2$ and 2 drops of DMF, stirred at 0 °C for 2 h, at room temperature for 1 h, and concentrated *in vacuo*. A solution of the residue in 40 mL of CH_2Cl_2 was cooled to -78 °C, treated with 10 mL of NH_3, slowly warmed to room temperature over 12 h, filtered and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (95:5, CH_2Cl_2/MeOH) to yield 261 mg (19%) of **218** as a colorless foam: mp 105-107 °C (MeOH/CH_2Cl_2); IR (thin film) 3407, 3217, 3053, 1591, 1436, 1184, 1120, 902, 824, 802, 783, 744, 692 cm^{-1}; ^1H NMR δ 7.69-7.61 (m, 8 H), 7.56-7.40 (m, 12 H); EIMS *m/z* 393 (M^+, 64), 375 (33), 277 (51), 252 (100), 77 (15); HRMS (EI) *m/z* calcd for $C_{26}H_{20}NOP$ 393.1283, found 393.1275.



219

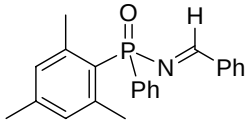
***N*-Benzylidene-*P*-2-(1,1'-binaphthyl)-*P*-phenylphosphinamide (219).** According to the General Protocol B, 220 mg (0.559 mmol) of phosphinamide **218**, 230 μL (1.65 mmol) of Et_3N, 90.0 μL (0.885 mmol) of PhCHO, and 35.0 μL (0.319 mmol) of $TiCl_4$ afforded a 1.8:1 mixture of diastereomers. The mixture was recrystallized from CH_2Cl_2/hexanes to yield 42 mg (16%) of **219** as a colorless solid: mp 204-205 °C (CH_2Cl_2/hexanes); IR (thin film) 3055, 1618, 1577, 1196, 1113, 852, 831, 752, 690 cm^{-1}; ^1H NMR δ 8.47 (d, 1 H, J = 33.2 Hz), 7.94-7.00 (m,

23 H); ESIMS *m/z* 504 ([M+Na]$^+$, 62), 482 ([M+H]$^+$, 100); HRMS (ESI) *m/z* calcd for $C_{33}H_{25}NOP$ [M+H] 482.1674, found 482.1652.



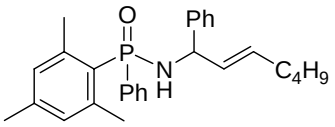
220

(*E*)-*P*-2-(1,1'-Binaphthyl)-*P*-phenyl-*N*-(1-phenylhept-2-enyl)phosphinamide (220). According to the General Protocol A, 28.0 mg (0.109 mmol) of Cp_2ZrHCl, 15.0 μL (0.131 mmol) of 1-hexyne, 27.0 mg (0.0561 mol) of imine **219**, and 50.0 μL (0.100 mmol) of Me_2Zn (2.0 M solution in toluene) afforded 24 mg (76%) of **220** as an (inseparable) 72:28 mixture of diastereomers: IR (thin film) 3381, 3207, 3055, 2954, 2924, 2858, 1452, 1439, 1184, 1113, 1026, 972, 783, 746, 696 cm^{-1}; ^{1}H NMR δ 8.01-6.83 (m, 23 H), 5.17-5.04 (m, 1.7 H), 4.91 (dtd, 0.3 H, *J* = 15.3, 6.6, 1.4 Hz), 4.50 (td, 0.7 H, *J* = 9.4, 4.2 Hz), 4.39 (td, 0.3 H, *J* = 9.9, 5.7 Hz), 2.88-2.79 (m, 1 H), 1.93-1.75 (m, 2 H), 1.24-1.08 (m, 4 H), 0.83 (t, 3 H, *J* = 6.8 Hz); ESIMS *m/z* 588 ([M+Na]$^+$, 70), 566 ([M+H]$^+$, 100); HRMS (ESI) *m/z* calcd for $C_{39}H_{37}NOP$ [M+H] 566.2613, found 566.2621.



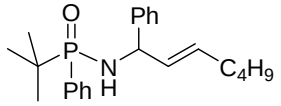
222

***N*-Benzylidene-*P*-mesityl-*P*-phenylphosphinamide (222).** According to the General Protocol B, 500 mg (1.93 mmol) of *P*-mesityl-*P*-phenylphosphinamide (**221**), 290 μL (2.85 mmol) of PhCHO, 810 μL (5.81 mmol) of Et_3N, and 120 μL (1.09 mmol) of $TiCl_4$ afforded 235 mg (35%) of **222** as a colorless solid: mp 166-167 °C (CH_2Cl_2/hexanes); IR (thin film) 3441, 3058, 2969, 2931, 1610, 1575, 1449, 1435, 1197, 1116, 850, 821, 753, 691, 645 cm^{-1}; ^{1}H NMR δ 9.32 (d, 1 H, *J* = 32.8 Hz), 7.97-7.93 (m, 2 H), 7.73-7.66 (m, 2 H), 7.55-7.37 (m, 6 H), 6.88-6.87 (m, 2 H), 2.53 (s, 6 H), 2.26 (s, 3 H); EIMS *m/z* 347 (M$^+$, 100), 270 (26), 256 (20), 243 (68), 106 (85), 91 (32), 77 (22); HRMS (EI) *m/z* calcd for $C_{22}H_{22}NOP$ 347.1439, found 347.1443.



223

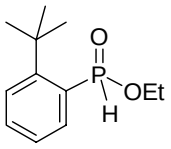
(*E*)-*P*-Mesityl-*P*-phenyl-*N*-(1-phenylhept-2-enyl)phosphinamide (223). According to the General Protocol A, 95.0 mg (0.368 mmol) of Cp_2ZrHCl, 50.0 μL (0.435 mmol) of 1-hexyne, 190 μL (0.380 mmol) of Me_2Zn, and 87.0 mg (0.250 mmol) of imine **222** afforded 57 mg (53%) of **223** as an (inseparable) 69:31 mixture of diastereomers: mp 122-125 °C (EtOAc/hexanes); IR (thin film) 3204, 2957, 2927, 2854, 1607, 1453, 1435, 1176, 1116, 748, 696 cm^{-1}; ^1H NMR δ 7.75-7.67 (m, 1.4 H), 7.60-7.53 (m, 0.6 H), 7.46-7.15 (m, 8 H), 6.87 (d, 0.6 H, *J* = 3.7 Hz), 6.80 (d, 1.4 H, *J* = 3.7 Hz), 5.77 (dd, 0.7 H, *J* = 15.3, 6.2 Hz), 5.66-5.54 (m, 1 H), 5.42 (dt, 0.3 H, *J* = 15.3, 6.6 Hz), 5.08 (td, 0.3 H, *J* = 8.9, 7.1 Hz), 4.97 (td, 0.7 H, *J* = 9.2, 6.4 Hz), 3.19 (t, 0.3 H, *J* = 9.1 Hz), 3.13 (t, 0.7 H, *J* = 8.9 Hz), 2.45 (s, 1.8 H), 2.35 (s, 4.2 H), 2.28 (s. 0.9 H), 2.26 (s, 2.1 H), 2.05 (q, 1.4 H, *J* = 6.7 Hz), 1.86 (q, 0.6 H, *J* = 6.7 Hz), 1.40-1.26 (m, 2.8 H), 1.23-1.14 (m, 1.2 H), 0.89 (t, 2.1 H, *J* = 7.1 Hz), 0.83 (t, 0.9 H, *J* = 6.8 Hz); ESIMS *m/z* 454 ($[M+Na]^+$, 100), 432 ($[M+H]^+$, 75); HRMS (ESI) *m/z* calcd for $C_{28}H_{34}NOPNa$ [M+Na] 454.2276, found 454.2280.



225

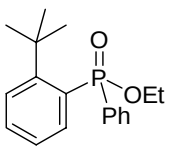
(*E*)-*P*-(*tert*-Butyl)-*P*-phenyl-*N*-(1-phenylhept-2-enyl)phosphinamide (225). According to the General Protocol B, 500 mg (2.54 mmol) of *P*-(*tert*-butyl)-*P*-phenylphosphinamide (**224**), 1.17 mL (8.39 mmol) of Et_3N, 390 μL (3.84 mmol) of PhCHO, and 150 μL (1.34 mmol) of $TiCl_4$ afforded a 1.6:1 mixture of imine and PhCHO, which was used without further purification in the subsequent reaction. According to the General Protocol A, 390 mg (1.51 mmol) of Cp_2ZrHCl, 200 μL (1.74 mmol) of 1-hexyne, 500 μL (1.00 mmol) of Me_2Zn, and 200 mg (0.571 mmol) of crude imine (81% purity) afforded 67 mg (32%) of **225** as an (inseparable) 69:31 mixture of diastereomers: IR (thin film) 3228, 2060, 2954, 2929, 2862, 1687, 1475, 1437, 1165, 1113, 1057, 748, 700 cm^{-1}; ^1H NMR δ 7.88-7.81 (m, 0.6 H), 7.64-7.58 (m, 1.4 H), 7.51-7.35 (m, 2 H), 7.33-7.13 (m, 6 H), 5.71 (ddt, 0.7 H, *J* = 15.4, 5.4, 1.3 Hz), 5.52-5.37 (m, 1.3 H), 4.79 (td, 0.3 H, *J* = 8.8, 5.7 Hz), 4.70 (td, 0.7 H, *J* = 9.5, 5.3 Hz), 2.98-2.89 (m, 1 H), 1.98 (q, 1.4 H, *J* = 7.0 Hz),

1.89 (q, 0.6 H, *J* = 6.2 Hz), 1.36-1.18 (m, 4 H), 1.12 (d, 6.3 H, *J* = 14.8 Hz), 1.09 (d, 2.7 H, *J* = 14.8 Hz), 0.85-0.80 (m, 3 H); ESIMS *m/z* 392 ([M+Na]$^+$, 68), 370 ([M+H]$^+$, 100); HRMS (ESI) *m/z* calcd for $C_{23}H_{33}NOP$ [M+H] 370.2300, found 370.2290.



244

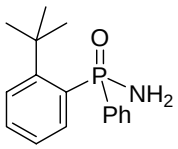
Ethyl (2-*tert*-butylphenyl)phosphinate (244). According to a literature procedure,[243] a suspension of 220 mg (9.05 mmol) of Mg in 10 mL of THF was treated with a solution of 2.00 g (9.38 mmol) of *ortho*-bromo-*tert*-butybenzene (**243**) in 10 mL of THF. The reaction was initiated with 2 drops of $(CH_2Br)_2$, and the mixture was heated at reflux for 2 h, cooled to room temperature, treated with a solution of 910 μL (5.66 mmol) of $ClP(OEt)_2$ (90% purity) in 10 mL of THF, heated at reflux for 2 h, cooled to room temperature, diluted with 30 mL of dioxane, filtered through Celite, and concentrated *in vacuo*. Kugelrohr distillation (120 °C, ~1 atm) of the residue afforded a colorless oil that was dissolved in 10 mL of THF, treated with 20 mL of 0.1 M HCl, stirred at 50 °C for 4 h, cooled to room temperature and extracted with CH_2Cl_2 (4x). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield 1.21 g (95%) of **244** as a colorless oil: IR (thin film) 2966, 2906, 2870, 1475, 1433, 1365, 1192, 1122, 1024, 960, 762 cm^{-1}; ^{1}H NMR δ 7.90 (d, 1 H, J = 566 Hz), 7.95-7.86 (m, 1 H), 7.55-7.43 (m, 2 H), 7.33-7.27 (m, 1 H), 4.24-4.04 (m, 2 H), 1.49 (s, 9 H), 1.33 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 153.88 (d, 1 C, *J* = 10.2 Hz), 133.00 (d, 1 C, *J* = 13.9 Hz), 132.55 (s, 1 C), 128.70 (d, 1 C, *J* = 126 Hz), 127.09 (d, 1 C, *J* = 12.8 Hz), 125.67 (d, 1 C, *J* = 14.7 Hz), 62.36 (d, 1 C, *J* = 6.1 Hz), 37.04 (s, 1 C), 32.32 (s, 3 C), 16.10 (d, 1 C, *J* = 6.4 Hz); EIMS *m/z* 226 (M$^+$, 52), 211 (43), 183 (80), 156 (58), 147 (100), 115 (49), 91 (77), 84 (42), 77 (54); HRMS (EI) *m/z* calcd for $C_{12}H_{19}O_2P$ 226.1123, found 226.1124.



245

Ethyl (2-*tert*-butylphenyl)phenylphosphinate (245). According to a literature procedure, a suspension of 1.00 g (4.42 mmol) of ethyl phosphinate **244**, 30.0 mg (0.134 mmol)

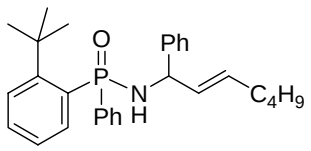
of $Pd(OAc)_2$, 320 mg (0.577 mmol) of dppf, 1.23 mL (8.82 mmol) of Et_3N, and 490 μL (4.38 mmol) of iodobenzene in 25 mL of MeCN was stirred at 70 °C for 24 h. The mixture was cooled to room temperature, diluted with EtOAc, filtered through Celite, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (50:50, hexanes/EtOAc) to yield 800 mg (60%) of **245** as an orange oil: IR (thin film) 2960, 2902, 2870, 1473, 1439, 1228, 1122, 1030, 947, 746, 696 cm^{-1}; ^1H NMR δ 7.95-7.87 (m, 1 H), 7.70-7.57 (m, 3 H), 7.47-7.34 (m, 4 H), 7.26-7.20 (m, 1 H), 4.12-4.02 (m, 2 H), 1.53 (s, 9 H), 1.32 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 156.53 (d, 1 C, *J* = 10.1 Hz), 136.11 (d, 1 C, *J* = 9.8 Hz), 134.37 (d, 1 C, *J* = 136 Hz), 131.93 (s, 1 C), 131.39 (s, 1 C), 131.33 (d, 2 C, *J* = 9.9 Hz), 128.70 (d, 1 C, *J* = 128. Hz), 128.21 (d, 2 C, *J* = 13.1 Hz), 127.65 (d, 1 C, *J* = 13.0 Hz), 125.08 (d, 1 C, *J* = 12.6 Hz), 60.73 (d, 1 C, *J* = 5.5 Hz), 37.22 (s, 1 C), 32.20 (s, 3 C), 16.33 (d, 1 C, *J* = 3.4 Hz); EIMS *m/z* 302 (M^+, 71), 287 (61), 259 (39), 217 (27), 202 (34), 163 (28), 141 (31), 115 (44), 91 (55), 77 (100); HRMS (EI) *m/z* calcd for $C_{18}H_{23}O_2P$ 302.1436, found 302.1444.



226

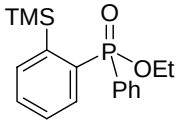
***P*-(2-*tert*-Butylphenyl)-*P*-phenylphosphinamide (226).** According to a literature procedure,[204] a solution of 200 mg (8.70 mmol) of Na in 30 mL of NH_3 was stirred at -35 °C for 1 h, treated with a solution of 760 mg (2.51 mmol) of ethyl phosphinate **245** in 10 mL of THF, stirred at -35 °C for 5 h and slowly warmed to room temperature over 12 h. The mixture was quenched with solid NH_4Cl then wet THF, poured into 1 N HCl, and extracted with CH_2Cl_2 (3x). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (50:50, hexanes/Et_2O) to yield 187 mg (27%) of **226** as a colorless solid: mp 139-140 °C (Et_2O, hexanes); IR (thin film) 3225, 3078, 2954, 1567, 1475, 1436, 1194, 1118, 893, 762, 750, 735, 695 cm^{-1}; ^1H NMR δ 7.91 (ddd, 1 H, *J* = 16.1, 7.8, 1.5 Hz), 7.79-7.72 (m, 2 H), 7.61-7.56 (m, 1 H), 7.48-7.35 (m, 4 H), 7.21-7.15 (m, 1 H), 3.05 (bs, 2 H), 1.57 (s, 9 H); ^{13}C NMR δ 156.63 (d, 1 C, *J* = 9.3 Hz), 136.70 (d, 1 C, *J* = 128.4 Hz), 136.63 (d, 1 C, *J* = 11.9 Hz), 131.78 (s, 1 C), 131.40 (d, 2 C, *J* = 9.2 Hz), 131.34 (s, 1 C), 131.01 (d, 1 C, *J* = 116.8 Hz), 128.43 (d, 2 C, *J* = 12.8 Hz), 127.79 (d, 1 C, *J* = 12.1 Hz), 125.20 (d, 1 C, *J* = 13.1 Hz),

37.51 (s, 1 C), 32.46 (s, 3 C); EIMS *m/z* 273 (M^+, 90), 258 (100), 241 (45), 199 (50), 163 (28), 91 (20), 77 (32); HRMS (EI) *m/z* calcd for $C_{16}H_{20}NOP$ 273.1283, found 273.1283.



227

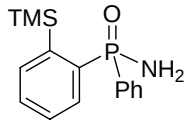
(*E*)-*P*-(2-*tert*-Butylphenyl)-*P*-phenyl-*N*-(1-phenylhept-2-enyl)phosphinamide (227). According to the General Protocol B, 166 mg (0.607 mmol) of phosphinamide **226**, 320 μL (1.84 mmol) of (*i*-Pr)$_2$NEt, 100 μL (0.984 mmol) of PhCHO, and 40.0 μL (0.365 mmol) of $TiCl_4$ afforded the crude imine, which was used without further purification in the subsequent reaction. According to the General Protocol A, 46.0 mg (0.178 mmol) of Cp_2ZrHCl, 23.0 μL (0.200 mmol) of 1-hexyne, 90.0 μL (0.180 mmol) of Me_2Zn (2.0 M solution in toluene), and 32.4 mg (0.0896 mmol) of crude imine at a reaction temperature of 40 °C afforded 27 mg (68%) of **227** as an (inseparable) 54:46 mixture of diastereomers: IR (thin film) 3213, 2922, 2870, 1589, 1435, 1197, 1113, 1051, 1028, 970, 924, 739, 702 cm^{-1}; ^1H NMR δ 7.94-7.55 (m, 4 H), 7.49-7.04 (m, 10 H), 5.75-5.44 (m, 2 H), 4.94-4.82 (m, 1 H), 2.99-2.89 (m, 1 H), 2.04-1.96 (m, 2 H), 1.61 (s, 4.9 H), 1.55 (s, 4.1 H), 1.30-1.15 (m, 4 H), 0.89-0.82 (m, 3 H); ESIMS *m/z* 468 ($[M+Na]^+$, 84), 446 ($[M+H]^+$, 100); HRMS (ESI) *m/z* calcd for $C_{29}H_{37}NOP$ [M+H] 446.2613, found 446.2603.



247

Ethyl [2-(trimethylsilyl)phenyl]phenylphosphinate (247). According to a literature procedure, a suspension of 190 mg (7.82 mmol) of Mg in 10 mL of THF was treated with a solution of 1.75 g (7.64 mmol) of (2-bromophenyl)trimethylsilane (**246**) in 10 mL of THF. The reaction was initiated with 2 drops of 1,2-dibromoethane, and the mixture was heated at reflux for 4 h, cooled to room temperature, treated with a solution of 1.23 mL (7.65 mmol) of $ClP(OEt)_2$ (90% purity) in 10 mL of THF, heated at reflux for 12 h, cooled to room temperature, diluted with 30 mL of dioxane, filtered through Celite, and concentrated *in vacuo*. Kugelrohr distillation (110 °C, ~1 atm) of the residue afforded a colorless oil that was dissolved in 10 mL of THF, treated with 20 mL of 0.1 M HCl, stirred at 60 °C for 6 h, cooled to room temperature and extracted with CH_2Cl_2 (4x). The combined organic extracts were dried ($MgSO_4$) and

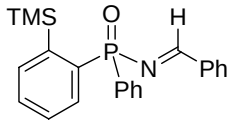
concentrated *in vacuo*. A suspension of the residue, 33.0 mg (0.147 mmol) of $Pd(OAc)_2$, 164 mg (0.296 mmol) of dppf, 770 μL (4.42 mmol) of (*i*-Pr)$_2$NEt, and 400 μL (3.57 mmol) of iodobenzene in 25 mL of MeCN was stirred at 70 °C for 18 h. The mixture was cooled to room temperature, diluted with EtOAc, filtered through Florisil, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (30:70, hexanes/EtOAc) to yield 646 mg (28%) of **247** as a yellow oil: IR (thin film) 3055, 2980, 2947, 2899, 1439, 1230, 1134, 1119, 1032, 949, 845, 742, 696 cm^{-1}; ^{1}H NMR δ 7.78-7.66 (m, 4 H), 7.49-7.37 (m, 5 H), 4.09-3.99 (m, 2 H), 1.31 (t, 3 H, *J* = 7.1 Hz), 0.38 (s, 9 H); ^{13}C NMR δ 145.84 (d, 1 C, *J* = 18.6 Hz), 136.18 (d, 1 C, *J* = 138.1 Hz), 136.04 (d, 1 C, *J* = 16.8 Hz), 133.33 (d, 1 C, *J* = 13.4 Hz), 132.77 (d, 1 C, *J* = 133.0 Hz), 131.74 (s, 1 C), 131.67 (d, 2 C, *J* = 10.1 Hz), 130.83 (d, 1 C, *J* = 3.1 Hz), 128.30 (d, 2 C, *J* = 12.9 Hz), 128.18 (d, 1 C, *J* = 13.4 Hz), 60.79 (d, 1 C, *J* = 5.8 Hz), 16.39 (d, 1 C, *J* = 6.7 Hz), 1.35 (s, 3 C); EIMS *m/z* 303 ([M-CH$_3$]$^+$, 100), 275 (86), 197 (29), 183 (24), 135 (22), 107 (18), 77 (21); HRMS (EI) *m/z* calcd for $C_{16}H_{20}O_2PSi$ [M-CH$_3$] 303.0970, found 303.0976.



228

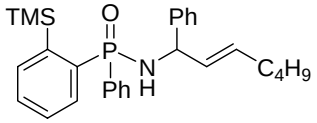
***P*-[2-(Trimethylsilyl)phenyl]-*P*-phenylphosphinamide (228).** A solution of 2.07 g (6.50 mmol) of ethyl phosphinate **247** in 50 mL of CH_2Cl_2 was treated with 1.72 mL (13.0 mmol) of TMS-Br.[244] The mixture was stirred at room temperature for 4 h, treated with 25 mL of MeOH, stirred at room temperature for 1 h, and concentrated *in vacuo*. A solution of the residue in 15 mL of CH_2Cl_2 was cooled to 0 °C, and treated with 1.13 mL (13.0 mmol) of $(COCl)_2$ and 3 drops of DMF. The mixture was stirred at 0 °C for 10 min, at room temperature for 5 h, and concentrated *in vacuo*. A solution of the residue in 50 mL of CH_2Cl_2 was cooled to -78 °C, treated with 10 mL of NH_3, slowly warmed to room temperature over 5 h, filtered, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (99:1, Et_2O/MeOH) to yield 1.65 g (88%) of **228** as a yellow solid: mp 141-142 °C (MeOH/Et_2O); IR (thin film) 3413, 3213, 3065, 1571, 1436, 1243, 1197, 1117, 896, 848, 758 cm^{-1}; ^{1}H NMR δ 7.88 (ddd, 1 H, *J* = 13.1, 7.5, 1.1 Hz), 7.82-7.74 (m, 3 H), 7.47-7.34 (m, 5 H), 3.12 (bs, 2 H), 0.36 (s, 9 H); ^{13}C NMR δ 146.14 (d, 1 C, *J* = 18.3 Hz), 138.26 (d, 1 C, *J* = 131.8 Hz), 136.14 (d, 1 C, *J* = 16.2 Hz), 134.74 (d, 1 C, *J* = 125.1 Hz), 133.71 (d, 1 C, *J* = 13.2 Hz), 131.70 (d, 2 C, *J* = 9.9 Hz), 131.47 (d, 1 C, *J*

= 2.2 Hz), 130.57 (d, 1 C, *J* = 2.7 Hz), 128.25 (d, 2 C, *J* = 12.5 Hz), 128.17 (d, 1 C, *J* = 12.8 Hz), 1.72 (s, 3 C); EIMS *m/z* 289 (M^+, 1), 288 (3), 274 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{17}NOPSi$ [M-CH_3] 274.0817, found 274.0944.



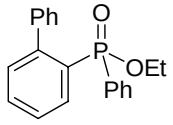
229

***N*-Benzylidene-*P*-[2-(trimethylsilyl)phenyl]-*P*-phenylphosphinamide (229).** According to the General Protocol B, 1.09 g (3.77 mmol) of phosphinamide **228**, 1.97 mL (11.3 mmol) of (*i*-Pr)$_2$NEt, 570 μL (5.61 mmol) of PhCHO, and 250 μL (2.28 mmol) of $TiCl_4$ afforded the crude imine, which was chromatographed on SiO_2 (80:20, hexanes/EtOAc, containing 2% Et_3N) to yield 1.23 g (87%) of **229** as a yellow glass: IR (thin film) 3057, 2945, 2895, 1703, 1618, 1577, 1452, 1437, 1242, 1205, 1113, 1057, 852, 822, 739, 688, 663 cm^{-1}; ^1H NMR δ 9.28 (d, 1 H, *J* = 31.4 Hz), 8.21 (ddd, 1 H, *J* = 12.0, 6.8, 2.0 Hz), 7.99 (d, 2 H, *J* = 6.8 Hz), 7.83-7.75 (m, 3 H), 7.59-7.38 (m, 8 H), 0.41 (s, 9 H); ESIMS *m/z* 400 ($[M+Na]^+$, 72), 378 ($[M+H]^+$, 58), 362 ($[M-CH_3]^+$, 100); HRMS (ESI) *m/z* calcd for $C_{22}H_{25}NOPSi$ [M+H] 378.1443, found 378.1452.



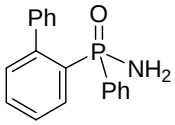
230

(*E*)-*P*-[2-(Trimethylsilyl)phenyl]-*P*-phenyl-*N*-(1-phenylhept-2-enyl)phosphinamide (230). According to the General Protocol A, 115 mg (0.446 mmol) of Cp_2ZrHCl, 56.0 μL (0.487 mmol) of 1-hexyne, 220 μL (0.440 mmol) of Me_2Zn (2.0 M solution in toluene), and 85.0 mg (0.225 mmol) of imine **229** afforded 73 mg (70%) of **230** as an (inseparable) 51:49 mixture of diastereomers: IR (thin film) 3333, 3059, 2957, 2929, 1691, 1452, 1437, 1243, 1191, 1116, 843, 754, 695 cm^{-1}; ^1H NMR δ 7.96-7.70 (m, 4 H), 7.51-7.22 (m, 10 H), 5.75-5.46 (m, 2 H), 4.88-4.76 (m, 1 H), 3.18-3.11 (m, 1 H), 1.99-1.95 (m, 2 H), 1.30-1.20 (m, 4 H), 0.90-0.85 (m, 3 H), 0.44 (s, 4.5 H), 0.42 (s, 4.5 H); EIMS *m/z* 461 (M^+, 13), 446 (56), 388 (14), 362 (18), 274 (100), 258 (54), 188 (85), 117 (52), 91 (41); HRMS (EI) *m/z* calcd for $C_{28}H_{36}NOPSi$ 461.2304, found 461.2312.



249

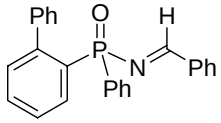
Ethyl (2-biphenyl)phenylphosphinate (249). According to a literature procedure, a suspension of 420 mg (17.3 mmol) of Mg in 40 mL of THF was treated with 4.00 g (17.2 mmol) of 2-bromobiphenyl (**248**). The reaction was initiated with 1 drop of $(CH_2Br)_2$, and the mixture was heated at reflux for 2 h, cooled to room temperature, treated with 1.80 mL (11.2 mmol) of $ClP(OEt)_2$ (90% purity), heated at reflux for 2 h, cooled to room temperature, diluted with 30 mL of dioxane, filtered through Celite, and concentrated *in vacuo*. Kugelrohr distillation (120 °C, ~1 atm) of the residue afforded a colorless oil that was dissolved in 20 mL of THF, treated with 40 mL of 0.1 M HCl, stirred at 50 °C for 3 h, cooled to room temperature and extracted with CH_2Cl_2 (4x). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. A suspension of the residue, 75.0 mg (0.334 mmol) of $Pd(OAc)_2$, 372 mg (0.671 mmol) of dppf, 2.90 mL (16.6 mmol) of $(i\text{-}Pr)_2NEt$, and 1.50 mL (13.4 mmol) of iodobenzene in 100 mL of MeCN was stirred at 70 °C for 16 h. The mixture was cooled to room temperature, diluted with EtOAc, filtered through Celite, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (1:2, hexanes/EtOAc) to yield 2.95 g (82%) of **249** as a pink solid: mp 115-116 °C (EtOAc/hexanes); IR (thin film) 3461, 3055, 2977, 1437, 1221, 1033, 951, 753, 696 cm^{-1}; ^1H NMR δ 8.04 (dd, 1 H, J = 12.2, 7.7 Hz), 7.50 (t, 1 H, J = 7.4 Hz), 7.41 (t, 1 H, J = 7.5 Hz), 7.36-7.28 (m, 3 H), 7.22-7.07 (m, 8 H), 3.99-3.78 (m, 2 H), 1.16 (t, 3 H, J = 7.0 Hz); ^{13}C NMR δ 146.46, 146.31, 140.71, 140.66, 132.95, 132.84, 131.69, 131.56, 131.37, 131.32, 131.22, 129.73, 127.91, 127.74, 127.22, 127.11, 126.72, 126.56, 60.49, 60.42, 16.21, 16.13; EIMS *m/z* 322 (M^+, 64), 321 (43), 293 (41), 277 (39), 245 (100), 217 (65), 199 (60), 152 (56); HRMS (EI) *m/z* calcd for $C_{20}H_{19}O_2P$ 322.1123, found 322.1113.



231

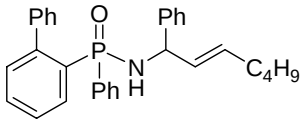
***P*-2-Biphenyl-*P*-phenylphosphinamide (231).** A solution of 2.50 g (7.76 mmol) of ethyl phosphinate **249** in 50 mL of CH_2Cl_2 was treated with 2.05 mL (15.5 mmol) of TMS-Br. The mixture was stirred at room temperature for 2 h, treated with 25 mL of MeOH, stirred at

room temperature for 1 h, and concentrated *in vacuo*. A solution of the residue in 15 mL of CH_2Cl_2 was cooled to 0 °C, and treated with 1.35 mL (15.5 mmol) of $(COCl)_2$ and 3 drops of DMF. The mixture was stirred at 0 °C for 1 h, at room temperature for 4 h, and concentrated *in vacuo*. A solution of the residue in 50 mL of CH_2Cl_2 was cooled to -78 °C, treated with 10 mL of NH_3, slowly warmed to room temperature over 5 h, filtered, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (95:5, Et_2O/ MeOH) to yield 2.15 g (95%) of **231** as a colorless solid: mp 149-150 °C (MeOH/Et_2O); IR (thin film) 3411, 3219, 3055, 1567, 1465, 1437, 1188, 1134, 1117, 898, 749, 697 cm^{-1}; ^1H NMR δ 7.85 (ddd, 1 H, *J* = 14.0, 7.7, 1.3 Hz), 7.59-7.19 (m, 13 H), 2.89 (bs, 2 H); ^{13}C NMR δ 144.94 (d, 1 C, *J* = 9.5 Hz), 140.99 (d, 1 C, *J* = 3.8 Hz), 134.05 (d, 1 C, *J* = 129.2 Hz), 132.61 (d, 1 C, *J* = 10.7 Hz), 132.58 (d, 1 C, *J* = 125.8 Hz), 131.63 (d, 2 C, *J* = 10.1 Hz), 131.44 (d, 1 C, *J* = 2.4 Hz), 131.11 (d, 1 C, *J* = 6.0 Hz), 131.02 (d, 1 C, *J* = 2.0 Hz), 129.57 (s, 2 C), 128.05 (d, 2 C, *J* = 12.8 Hz), 127.89 (s, 2 C), 127.67 (s, 1 C), 126.86 (d, 1 C, *J* = 12.7 Hz); EIMS *m/z* 293 (M^+, 37), 292 (43), 275 (36), 216 (100), 199 (63), 152 (26); HRMS (EI) *m/z* calcd for $C_{18}H_{16}NOP$ 293.0970, found 293.0983.



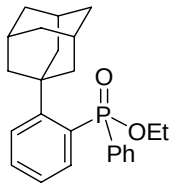
232

***N*-Benzylidene-*P*-2-biphenyl-*P*-phenylphosphinamide (232).** According to the General Protocol B, 1.15 g (3.92 mmol) of phosphinamide **231**, 2.05 mL (11.8 mmol) of (*i*-Pr)$_2$NEt, 600 μL (5.90 mmol) of PhCHO, and 260 μL (2.37 mmol) of $TiCl_4$ afforded the crude imine, which was chromatographed on SiO_2 (20:80, hexanes/EtOAc, containing 2% Et_3N) to yield 1.23 g (82%) of **232** as a colorless solid: mp 54-57 °C (solvent); IR (thin film) 3445, 3055, 1615, 1450, 1438, 1201, 1115, 852, 829, 752, 693 cm^{-1}; ^1H NMR δ 8.79 (d, 1 H, *J* = 32.6 Hz), 7.74-7.64 (m, 5 H), 7.51-7.22 (m, 11 H), 7.12-7.09 (m, 3 H); ESIMS *m/z* 404 ($[M+Na]^+$, 100), 382 ($[M+H]^+$, 26); HRMS (ESI) *m/z* calcd for $C_{25}H_{20}NOPNa$ [M+Na] 404.1180, found 404.1187.



233

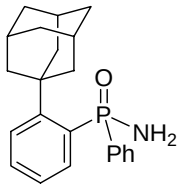
(*E*)-*P*-2-Biphenyl-*P*-phenyl-*N*-(1-phenylhept-2-enyl)phosphinamide (233). According to the General Protocol A, 135 mg (0.523 mmol) of Cp_2ZrHCl, 66.0 μL (0.574 mmol) of 1-hexyne, 260 μL (0.520 mmol) of Me_2Zn (2.0 M solution in toluene), and 100 mg (0.262 mmol) of imine **232** at a reaction temperature of 40 °C afforded 109 mg (89%) of **233** as an (inseparable) 65:35 mixture of diastereomers: mp 101-104 °C (EtOAc/hexanes); IR (thin film) 3197, 3058, 2955, 2925, 2857, 1465, 1436, 1188, 1115, 753, 697 cm^{-1}; ^1H NMR δ 7.75-7.64 (m, 2 H), 7.54-7.15 (m, 15 H), 7.04 (dd, 1.3 H, *J* = 7.5, 1.7 Hz), 6.93 (dd, 0.7 H, *J* = 7.2, 2.1 Hz), 5.38-5.25 (m, 1.65 H), 5.16 (dt, 0.35 H, *J* = 15.3, 6.6 Hz), 4.73-4.61 (m, 1 H), 2.82-2.73 (m, 1 H), 1.90-1.80 (m, 2 H), 1.27-1.18 (m, 4 H), 0.90-0.83 (m, 3 H); EIMS *m/z* 465 (M^+, 21), 292 (23), 277 (59), 199 (53), 188 (100); HRMS (EI) *m/z* calcd for $C_{31}H_{32}NOP$ 465.2222, found 465.2235.



251

Ethyl [2-(1-adamantyl)phenyl]phenylphosphinate (251). According to a literature procedure, a suspension of 190 mg (7.82 mmol) of Mg in 40 mL of THF was treated with 2.29 g (7.86 mmol) of 1-(2-bromophenyl)adamantane (**250**). The reaction was initiated with 3 drops of $(CH_2Br)_2$, and the mixture was heated at reflux for 6 h, cooled to 0 °C, treated with 1.05 mL (6.53 mmol) of $ClP(OEt)_2$ (90% purity), heated at 40 °C for 12 h, cooled to room temperature, diluted with 30 mL of dioxane, filtered through Celite, and concentrated *in vacuo*. Kugelrohr distillation (130 °C, ~1 atm) of the residue afforded a colorless oil that was dissolved in 20 mL of THF, treated with 40 mL of 0.1 M HCl, stirred at 50 °C for 3 h, cooled to room temperature and extracted with CH_2Cl_2 (3x). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. A suspension of the residue, 45.0 mg (0.200 mmol) of $Pd(OAc)_2$, 217 mg (0.391 mmol) of dppf, 1.71 mL (9.82 mmol) of $(i\text{-Pr})_2NEt$, and 880 μL (7.86 mmol) of iodobenzene in 75 mL of MeCN was stirred at 70 °C for 16 h. The mixture was cooled to room

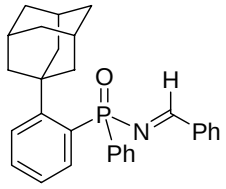
temperature, diluted with hexanes/EtOAc (1:1), filtered through Celite, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (2:1, hexanes/EtOAc) to yield 1.20 g (48%) of **251** as an orange solid: mp 129-130 °C (EtOAc/hexanes); IR (thin film) 2901, 2848, 1437, 1226, 1125, 1031, 947, 750, 725, 693 cm^{-1}; ^1H NMR δ 7.97 (ddd, 1 H, *J* = 14.6, 7.9, 1.5 Hz), 7.69-7.57 (m, 3 H), 7.53-7.34 (m, 4 H), 7.29-7.23 (m, 1 H), 4.21-4.02 (m, 2 H), 2.32 (d, 3 H, *J* = 12.1 Hz), 2.24 (d, 3 H, *J* = 12.1 Hz), 2.08 (s, 3 H), 1.85 (d, 3 H, *J* = 11.3 Hz), 1.71 (d, 3 H, *J* = 11.9 Hz), 1.36 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 157.58 (d, 1 C, *J* = 10.6 Hz), 136.48 (d, 1 C, *J* = 9.7 Hz), 135.09 (d, 1 C, *J* = 138.1 Hz), 132.02 (d, 1 C, *J* = 2.5 Hz), 131.24 (s, 1 C), 131.17 (s, 2 C, *J* = 9.7 Hz), 128.78 (d, 1 C, *J* = 125.6 Hz), 128.16 (d, 2 C, *J* = 13.1 Hz), 127.19 (d, 1 C, *J* = 13.3 Hz), 124.97 (d, 1 C, *J* = 12.8 Hz), 60.73 (d, 1 C, *J* = 5.8 Hz), 42.57 (s, 3 C), 39.03 (s, 1 C), 36.46 (s, 3 C), 29.38 (s, 3 C), 16.39 (d, 1 C, *J* = 6.8 Hz); EIMS *m/z* 380 (M^+, 20), 348 (29), 85 (65), 83 (99), 71 (100); HRMS (EI) *m/z* calcd for $C_{24}H_{29}O_2P$ 380.1905, found 380.1904.



234

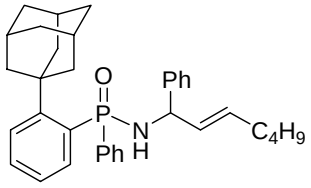
***P*-2-(1-Adamantyl)phenyl-*P*-phenylphosphinamide (234).** A solution of 1.16 g (3.05 mmol) of ethyl phosphinate **251** in 25 mL of CH_2Cl_2 was treated with 760 μL (5.76 mmol) of TMS-Br. The mixture was stirred at room temperature for 5 h, treated with 20 mL of MeOH, stirred at room temperature for 30 min, and concentrated *in vacuo*. A solution of the residue in 10 mL of CH_2Cl_2 was cooled to 0 °C, treated with 530 μL (6.08 mmol) of $(COCl)_2$ and 5 drops of DMF, stirred at 0 °C for 15 min, room temperature for 4 h, and concentrated *in vacuo*. A solution of the residue in 40 mL of CH_2Cl_2 was cooled to -78 °C, treated with 10 mL of NH_3, slowly warmed to room temperature over 6 h, filtered, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (50:50, CH_2Cl_2/Et_2O) to yield 656 mg (61%) of **234** as a colorless solid: mp 216-217 °C (CH_2Cl_2/Et_2O); IR (thin film) 2899, 2846, 1564, 1435, 1191, 1115, 890, 749, 693 cm^{-1}; ^1H NMR δ 7.80 (dd, 2 H, *J* = 12.3, 7.9 Hz), 7.71 (dd, 1 H, *J* = 16.8, 7.8 Hz), 7.58 (t, 1 H, *J* = 7.0 Hz), 7.50-7.42 (m, 4 H), 7.15 (t, 1 H, *J* = 7.5 Hz), 2.96 (bs, 2 H), 2.38 (s, 6 H), 2.13 (s, 3 H), 1.90 (bd, 3 H, *J* = 11.3 Hz), 1.74 (bd, 3 H, *J* = 11.7 Hz); ^{13}C NMR δ 157.42 (d, 1 C, *J* = 9.0 Hz), 137.20 (d, 1 C, *J* = 134.4 Hz), 136.39 (d, 1 C, *J* = 13.3 Hz), 131.61 (d, 1 C, *J* =

2.2 Hz), 131.14 (d, 2 C, J = 9.7 Hz), 131.08 (s, 1 C), 131.07 (d, 1 C, J = 117.1 Hz), 128.30 (d, 2 C, J = 12.9 Hz), 127.12 (d, 1 C, J = 12.3 Hz), 124.85 (d, 1 C, J = 13.6 Hz), 42.71 (s, 3 C), 39.06 (s, 1 C), 36.50 (s, 3 C), 29.46 (s, 3 C); ESIMS *m/z* 413 ($[M+Na+K]^{2+}$, 27), 374 ($[M+Na]^{+}$, 100), 335 (32); HRMS (ESI) *m/z* calcd for $C_{22}H_{26}NOPNa$ [M+Na] 374.1650, found 374.1665.



235

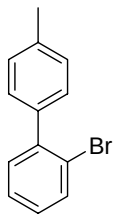
***P*-2-(1-Adamantyl)phenyl-*N*-benzylidene-*P*-phenylphosphinamide (235).** According to the General Protocol B, 620 mg (1.76 mmol) of phosphinamide **234**, 920 μL (5.28 mmol) of $(i\text{-Pr})_2NEt$, 270 μL (2.66 mmol) of PhCHO, and 120 μL (1.09 mmol) of $TiCl_4$ afforded the crude imine, which was chromatographed on SiO_2 (80:20, hexanes/EtOAc, containing 2% Et_3N) to yield 749 mg (97%) of **235** as a colorless solid: mp 172-173 °C (EtOAc/hexanes); IR (thin film) 2899, 2848, 1617, 1578, 1452, 1206, 1113, 817, 754, 691 cm^{-1}; ^1H NMR δ 9.29 (d, 1 H, J = 30.9 Hz), 8.42 (ddd, 1 H, J = 14.8, 7.9, 1.4 Hz), 8.00 (d, 2 H, J = 8.3 Hz), 7.74-7.35 (m, 10 H), 7.31-7.25 (m, 1 H), 2.32 (bs, 6 H), 2.10 (s, 3 H), 1.89 (d, 3 H, J = 11.3 Hz), 1.73 (d, 3 H, J = 11.9 Hz); ESIMS *m/z* 462 ($[M+Na]^{+}$, 100), 440 ($[M+H]^{+}$, 72; HRMS (ESI) *m/z* calcd for $C_{29}H_{31}NOP$ [M+H] 440.2143, found 440.2147.



236

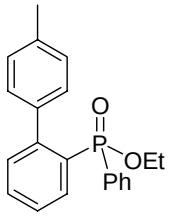
(*E*)-*P*-2-(1-Adamantyl)phenyl-*P*-phenyl-*N*-(1-phenylhept-2-enyl)phosphinamide (236). According to the General Protocol A, 117 mg (0.454 mmol) of Cp_2ZrHCl, 60.0 μL (0.522 mmol) of 1-hexyne, 230 μL (0.460 mmol) of Me_2Zn (2.0 M solution in toluene), and 100 mg (0.228 mmol) of imine **235** at a reaction temperature of 40 °C afforded 103 mg (86%) of **236** as an (inseparable) 59:41 mixture of diastereomers: mp 138-140 °C (EtOAc/hexanes); IR (thin film) 2901, 2846, 1433, 1186, 1113, 755, 696 cm^{-1}; ^1H NMR δ 7.87-7.01 (m, 14 H), 5.78-5.45 (m, 2 H), 5.06-4.91 (m, 1 H), 3.04-2.93 (m, 1 H), 2.39 (s, 2.4 H), 2.29 (s, 3.6 H), 2.12-1.67 (m,

11 H), 1.37-1.22 (m, 4 H), 0.93-0.83 (m, 3 H); ESIMS *m/z* 546 ([M+Na]$^+$, 100), 335 (15); HRMS (ESI) *m/z* calcd for $C_{35}H_{42}NOPNa$ [M+Na] 546.2902, found 546.2914.



252

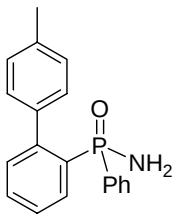
2-Bromo-4'-methylbiphenyl (252). A solution of 4.88 g (28.5 mmol) of 4-bromotoluene (**254**) in 125 mL of THF was cooled to -78 °C and treated with 12.0 mL (30.0 mmol) of *n*-BuLi (2.5 M solution in hexanes). The mixture was stirred at -78 °C for 30 min, treated with 6.70 mL (58.7 mmol) of $B(OMe)_3$, slowly warmed to room temperature over 16 h, quenched with saturated NH_4Cl, diluted with Et_2O, washed with 1 N HCl and brine, dried ($MgSO_4$), and concentrated *in vacuo*. According to a literature procedure,[245] a solution of the residue in 50 mL of DME and 100 mL of H_2O was treated with 3.50 mL (29.0 mmol) of 1,2-dibromobenzene (**255**), 11.8 g (85.4 mmol) of K_2CO_3, and 1.65 g (1.43 mmol) of $Pd(PPh_3)_4$. The mixture was heated at reflux for 12 h, cooled to room temperature and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with H_2O and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (99:1, hexanes/Et_2O) to yield 4.86 g (69%) of **252** as a colorless oil: IR (neat) 3053, 3027, 2918, 1464, 1434, 1027, 1005, 818, 753 cm^{-1}; ^{1}H NMR δ 7.71 (d, 1 H, *J* = 7.6 Hz), 7.40-7.35 (m, 4 H), 7.29 (d, 2 H, *J* = 7.9 Hz), 7.25-7.20 (m, 1 H), 2.46 (s, 3 H); ^{13}C NMR δ 142.57, 138.23, 137.28, 133.04, 131.27, 129.20 (2 C), 128.64 (2 C), 128.45, 127.27, 122.72, 21.20; EIMS *m/z* 248 (^{81}Br-M$^+$, 92), 246 (^{79}Br-M$^+$, 100), 167 (42), 165 (83), 152 (35); HRMS (EI) *m/z* calcd for $C_{13}H_{11}{}^{79}Br$ 246.0044, found 246.0043.



253

Ethyl [2-(4'-methylbiphenyl)]phenylphosphinate (253). According to a literature procedure, a suspension of 410 mg (16.9 mmol) of Mg in 50 mL of THF was treated with 4.20 g (17.0 mmol) of aryl bromide **252**. The reaction was initiated with 2 drops of $(CH_2Br)_2$, and the

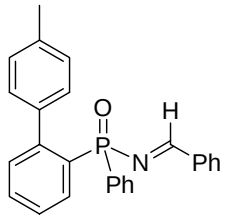
mixture was heated at reflux for 3 h, cooled to 0 °C, treated with 1.82 mL (11.3 mmol) of $ClP(OEt)_2$ (90% purity), heated at reflux at 4 h, cooled to room temperature, diluted with 100 mL of dioxane, filtered through Celite, and concentrated *in vacuo*. Kugelrohr distillation (120 °C, ~1 atm) of the residue afforded a colorless oil that was dissolved in 20 mL of THF, treated with 40 mL of 0.1 M HCl, stirred at 50 °C for 2 h, cooled to room temperature and extracted with CH_2Cl_2 (3x). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. A suspension of the residue, 76.0 mg (0.339 mmol) of $Pd(OAc)_2$, 377 mg (0.608 mmol) of dppf, 2.40 mL (17.2 mmol) of $(i\text{-Pr})_2NEt$, and 1.52 mL (13.6 mmol) of iodobenzene in 100 mL of MeCN was stirred at 70 °C for 16 h. The mixture was cooled to room temperature, diluted with hexanes/EtOAc (1:1), filtered through Celite, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (1:2, hexanes/EtOAc) to yield 2.04 g (54%) of **253** as a yellow oil: IR (thin film) 3463, 3053, 2980, 1466, 1436, 1223, 1134, 1119, 1033, 948, 817, 763, 750, 693 cm^{-1}; ^1H NMR δ 8.06 (ddd, 1 H, J = 12.9, 7.6, 1.3 Hz), 7.54-7.18 (m, 8 H), 6.99 (s, 4 H), 4.01-3.84 (m, 2 H), 2.34 (s, 3 H), 1.21 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 146.41 (d, 1 C, J = 11.4 Hz), 137.73 (d, 1 C, J = 4.3 Hz), 136.73 (s, 1 C), 132.85 (d, 1 C, J = 9.0 Hz), 132.23 (d, 1 C, J = 116.3 Hz), 131.57 (d, 2 C, J = 10.3 Hz), 131.57 (d, 1 C, J = 2.8 Hz), 131.33 (d, 1 C, J = 8.1 Hz), 131.23 (s, 1 C), 129.54 (s, 2 C), 128.73 (d, 1 C, J = 137.3 Hz), 127.86 (s, 2 C), 127.69 (d, 2 C, J = 13.2 Hz), 126.46 (d, 1 C, J = 12.4 Hz), 60.39 (d, 1 C, J = 5.6 Hz), 21.10 (s, 1 C), 16.16 (d, 1 C, J = 6.8 Hz); ESIMS *m/z* 359 ($[M+Na]^+$, 100), 337 ($[M+H]^+$, 13); HRMS (ESI) *m/z* calcd for $C_{21}H_{21}O_2Pna$ [M+Na] 359.1177, found 359.1168.



237

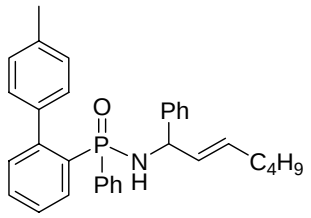
***P*-2-(4'-Methylbiphenyl)-*P*-phenylphosphinamide (237).** A solution of 2.02 g (6.01 mmol) of ethyl phosphinate **253** in 50 mL of CH_2Cl_2 was treated with 1.59 mL (12.0 mmol) of TMS-Br. The mixture was stirred at room temperature for 2 h, treated with 25 mL of MeOH, stirred at room temperature for 1 h, and concentrated *in vacuo*. A solution of the residue in 15 mL of CH_2Cl_2 was cooled to 0 °C, treated with 1.05 mL (12.0 mmol) of $(COCl)_2$ and 3 drops of DMF, stirred at 0 °C for 1 h, at room temperature for 4 h, and concentrated *in vacuo*. A solution

of the residue in 20 mL of CH_2Cl_2 was cooled to -78 °C and treated with 10 mL of NH_3, slowly warmed to room temperature over 12 h, filtered, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (95:5, Et_2O/MeOH) to yield 1.60 g (87%) of **237** as a colorless solid: mp 93-97 °C (MeOH/Et_2O); IR (thin film) 3420, 3225, 3046, 1591, 1563, 1464, 1437, 1191, 1134, 1119, 899, 819, 763, 694 cm^{-1}; ^1H NMR δ 7.77 (ddd, 1 H, *J* = 14.2, 7.7, 1.2 Hz), 7.63 (ddt, 2 H, *J* = 12.5, 6.9, 1.3 Hz), 7.52-7.44 (m, 2 H), 7.40-7.32 (m, 3 H), 7.26 (ddd, 1 H, *J* = 7.5, 4.6, 1.1 Hz), 7.17 (d, 2 H, *J* = 8.0 Hz), 7.12 (d, 2 H, *J* = 8.2 Hz), 2.65 (bs, 2 H), 2.38 (s, 3 H); ^{13}C NMR δ 144.76 (d, 1 C, *J* = 8.9 Hz), 138.10 (d, 1 C, *J* = 3.8 Hz), 137.60 (s, 1 C), 134.05 (d, 1 C, *J* = 129.3 Hz), 132.65 (d, 1 C, *J* = 132.6 Hz), 132.52 (d, 1 C, *J* = 11.2 Hz), 131.77 (d, 2 C, *J* = 9.9 Hz), 131.54 (d, 1 C, *J* = 3.0 Hz), 131.14 (d, 1 C, *J* = 11.5 Hz), 131.02 (d, 1 C, *J* = 2.4 Hz), 129.41 (s, 2 C), 128.73 (s, 2 C), 128.08 (d, 2 C, *J* = 12.9 Hz), 126.72 (d, 1 C, *J* = 12.8 Hz), 21.18 (s, 1 C); ESIMS *m/z* 346 ($[M+K]^+$, 6), 330 ($[M+Na]^+$, 100), 291 (12); HRMS (ESI) *m/z* calcd for $C_{19}H_{18}NOPNa$ [M+Na] 330.1024, found 330.1009.



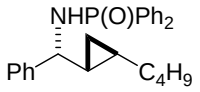
238

***N*-Benzylidene-*P*-2-(4'-methylbiphenyl)-*P*-phenylphosphinamide (238).** According to the General Protocol B, 1.01 g (3.29 mmol) of phosphinamide **237**, 400 μL (3.94 mmol) of PhCHO, 1.70 mL (9.76 mmol) of (*i*-Pr)$_2$NEt, and 210 μL (1.91 mmol) of $TiCl_4$ afforded the crude imine, which was chromatographed on SiO_2 (40:60, hexanes/EtOAc, containing 2% Et_3N) to yield 1.15 g (88%) of **238** as a colorless solid: mp 145-146 °C (EtOAc/hexanes); IR (thin film) 3439, 3055, 1612, 1575, 1467, 1452, 1436, 1201, 1132, 1114, 851, 828, 760, 693 cm^{-1}; ^1H NMR δ 8.73 (d, 1 H, *J* = 32.8 Hz), 7.81-7.26 (m, 14 H), 7.19 (d, 2 H, *J* = 8.1 Hz), 6.91 (d, 2 H, *J* = 7.7 Hz), 2.18 (s, 3 H); ESIMS *m/z* 813 ($[2M+Na]^+$, 100), 418 ($[M+Na]^+$, 88), 396 ($[M+H]^+$, 20); HRMS (ESI) *m/z* calcd for $C_{26}H_{22}NOPNa$ 418.1337, found 418.1337.



239

(*E*)-*P*-2-(4'-Methylbiphenyl)-*P*-phenyl-*N*-(1-phenylhept-2-enyl)phosphinamide (239). According to the General Protocol B, 98.0 mg (0.380 mmol) of Cp_2ZrHCl, 52.0 μL (0.453 mmol) of 1-hexyne, 130 μL (0.260 mmol) of Me_2Zn (2.0 M solution in toluene), and 100 mg (0.253 mmol) of imine **238** at a reaction temperature of 45 °C afforded 105 mg (87%) of **239** as an (inseparable) 63:37 mixture of diastereomers: IR (thin film) 3059, 2957, 2927, 2871, 1691, 1453, 1435, 1184, 1110, 817, 762, 696 cm^{-1}; ^1H NMR δ 7.77-7.12 (m, 15 H), 7.07-7.01 (m, 2 H), 6.93-6.89 (m, 1 H), 5.38-5.13 (m, 2 H), 4.68-4.60 (m, 1 H), 2.86-2.76 (m, 1 H), 2.41 (s, 1.2 H), 2.32 (s, 1.8 H), 1.92-1.81 (m, 2 H), 1.29-1.13 (m, 4 H), 0.89-0.83 (m, 3 H); ESIMS *m/z* 518 ($[M+K]^+$, 11), 502 ($[M+Na]^+$, 100), 291 (15); HRMS (ESI) *m/z* calcd for $C_{32}H_{34}NOPNa$ [M+Na] 502.2276, found 502.2299.



257

***N*-{(*R**)-[(1*R**,2*R**)-2-Butylcyclopropyl](phenyl)methyl}-*P*,*P*-diphenylphosphinamide (257).** A suspension of 389 mg (1.51 mmol) of Cp_2ZrHCl in 2.5 mL of CH_2Cl_2 was treated with 200 μL (1.74 mmol) of 1-hexyne. After 5 min, the yellow solution was cooled to -78 °C, treated with 750 μL (1.50 mmol) of Me_2Zn (2.0 M solution in toluene), warmed to room temperature over a period of 5 min, treated with a solution of 155 mg (0.508 mmol) of imine **104** in 1.5 mL of CH_2Cl_2, heated at reflux for 16 h, quenched with saturated $NaHCO_3$, diluted with EtOAc, filtered through Celite, washed with H_2O and brine, dried ($MgSO_4$), filtered through a pad of Florisil, and concentrated *in vacuo*. The residue was chromatographed on deactivated SiO_2 (1:3, hexanes/EtOAc containing 1% Et_3N) to yield 119 mg (58%) of **257** as a colorless solid and 21 mg (11%) of **146** as a colorless solid. **257**: mp 150-151 °C (EtOAc/hexane); IR (KBr) 3185, 3059, 2957, 2923, 2856, 1456, 1437, 1183, 1123, 1110, 1086, 1065, 724, 698 cm^{-1}; ^1H NMR δ 7.97-7.90 (m, 2 H), 7.80-7.73 (m, 2 H), 7.53-7.40 (m, 4 H), 7.36-7.22 (m, 7 H), 3.80 (q, 1 H, *J* = 8.9 Hz), 3.33 (t, 1 H, *J* = 6.6 Hz), 1.36-1.29 (m, 5 H), 1.10-0.98 (m, 2 H), 0.89 (t, 3

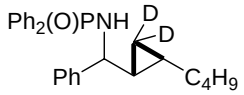
H, J = 7.0 Hz), 0.78-0.72 (m, 1 H), 0.41 (dt, 1 H, J = 8.6, 4.8 Hz), 0.26 (dt, 1 H, J = 8.3, 5.0 Hz); ^{13}C NMR δ 143.37, 143.30, 134.30, 133.15, 132.60, 132.42, 132.29, 131.96, 131.84, 131.71, 131.67, 131.57, 131.54, 131.43, 128.42, 128.29, 128.23, 128.09, 127.74, 127.62, 126.96, 126.77, 58.84, 33.22, 31.69, 26.85, 26.79, 22.52, 18.92, 14.10, 10.61; EIMS *m/z* 403 (M^+, 7), 360 (3), 319 (17), 306 (81), 256 (27), 201 (100), 91 (36), 77 (37); HRMS (EI) *m/z* calcd for $C_{26}H_{30}NOP$ 403.2065, found 403.2066.

Preparation of 257 in the presence of Diiodomethane. General Protocol C.

A suspension of 390 mg (1.51 mmol) of Cp_2ZrHCl in 2 mL of CH_2Cl_2 was treated with 190 μL (1.65 mmol) of 1-hexyne. After 5 min, the yellow solution was cooled to -78 °C, treated with 750 μL (1.50 mmol) of Me_2Zn (2.0 M solution in toluene), warmed to room temperature over a period of 5 min, treated with a solution of 153 mg (0.501 mmol) of imine **104** in 2 mL of CH_2Cl_2, and heated at reflux for 1 h. The mixture was cooled to room temperature, treated with 200 μL (2.48 mmol) of CH_2I_2, heated at reflux for a further 2 h, quenched with saturated NH_4Cl, diluted with EtOAc, washed with 1N HCl and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on deactivated SiO_2 (1:9, hexanes/EtOAc containing 1% Et_3N) to yield 149 mg (74%) of **257** [*dr* = 97:3 (HPLC)] as a colorless solid.

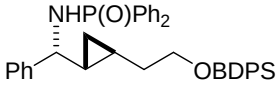
Preparation of 257 in the presence of Diiodomethane and Benzyl Alcohol.

A suspension of 390 mg (1.51 mmol) of Cp_2ZrHCl in 2 mL of CH_2Cl_2 was treated with 200 μL (1.74 mmol) of 1-hexyne. After 5 min, the yellow solution was cooled to -78 °C, treated with 1.00 mL (2.00 mmol) of Me_2Zn (2.0 M solution in toluene), warmed to room temperature over a period of 5 min, treated with a solution of 153 mg (0.501 mmol) of imine **104** and 55.0 mg (0.509 mmol) of $PhCH_2OH$ in 2 mL of CH_2Cl_2, and heated at reflux for 90 min. The mixture was cooled to room temperature, treated with 200 μL (2.48 mmol) of CH_2I_2, heated at reflux for a further 3 h, quenched with saturated $NaHCO_3$, diluted with EtOAc, filtered through Celite, washed with H_2O and brine, dried ($MgSO_4$), filtered through a pad of Florisil, and concentrated *in vacuo*. The residue was chromatographed on deactivated SiO_2 (1:9, hexanes/EtOAc containing 1% Et_3N) to yield 183 mg (91%) of **257** as a colorless solid.



258

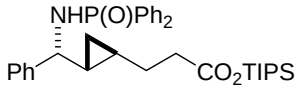
***N*-{(*R**)-[(1*R**,2*R**)-2-Butyl-3,3-bisdeuterocyclopropyl](phenyl)methyl}-*P*,*P*-diphenylphosphinamide (258).** A suspension of 192 mg (0.745 mmol) of Cp_2ZrHCl in 1.2 mL of CD_2Cl_2 was treated at room temperature with 95.0 μL (0.827 mmol) of 1-hexyne. After 5 min, the yellow solution was cooled to -78 °C, treated with 380 μL (0.760 mmol) of Me_2Zn (2.0 M solution in toluene), warmed to room temperature over a period of 5 min, treated with a solution of 78.0 mg (0.255 mmol) of imine **104** in 2 mL of CD_2Cl_2, and heated at reflux for 16 h, cooled to room temperature, quenched with saturated NH_4Cl, diluted with EtOAc, washed with 1 N HCl and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on deactivated SiO_2 (1:4, hexanes/EtOAc containing 1% Et_3N) to yield 35 mg (34%) of **258** as a colorless solid: mp 151-152 °C (EtOAc/hexane); IR (KBr) 3176, 2954, 2922, 2851, 1437, 1185, 1124, 1110, 1083, 1062 cm^{-1}; ^1H NMR δ 7.93-7.86 (m, 2 H), 7.76-7.69 (m, 2 H), 7.51-7.36 (m, 4 H), 7.32-7.18 (m, 7 H), 3.76 (q, 1 H, *J* = 8.9 Hz), 3.37 (dd, 1 H, *J* = 8.4, 6.0 Hz), 1.32-1.20 (m, 5 H), 1.06-0.95 (m, 2 H), 0.85 (t, 3 H, *J* = 7.0 Hz), 0.79-0.66 (m, 1 H); ^{13}C NMR δ 143.34, 143.28, 134.20, 133.07, 132.51, 132.38, 132.25, 131.93, 131.80, 131.69, 131.65, 131.55, 131.52, 131.35, 128.43, 128.26, 128.23, 128.20, 128.06, 126.93, 126.73, 58.76, 33.12, 31.68, 26.62, 26.56, 22.49, 18.67, 14.08, 9.94; ^2H NMR (77 MHz) δ 0.35, 0.20; EIMS *m/z* 405 (M^+, 9), 319 (28), 306 (85), 258 (45), 204 (45), 201 (100), 106 (21), 77 (37); HRMS (EI) *m/z* calcd for $C_{26}H_{38}D_2NOP$ 405.2191, found 405.2179.



259

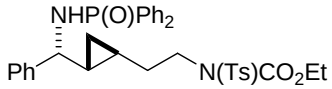
***N*-{(*R**)-[(1*S**,2*R**)-2-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}cyclopropyl](phenyl)-methyl}-*P*,*P*-diphenylphosphinamide (259).** According to the General Protocol C, 390 mg (1.51 mmol) of Cp_2ZrHCl, 531 mg (1.72 mmol) of alkyne **148**, 750 μL (1.50 mmol) of Me_2Zn (2.0 M solution in toluene), 153 mg (0.501 mmol) of imine **104** (2 h reaction time), and 200 μL (2.48 mmol) of CH_2I_2 (12 h reaction time) afforded 216 mg (68%) of **259** [*dr* = 98:2 (HPLC)] as a colorless oil: IR (neat) 3189, 3070, 2930, 2857, 1456, 1437, 1428, 1390, 1191, 1123, 1068, 1028, 823, 722, 694 cm^{-1}; ^1H NMR δ 7.95-7.87 (m, 2 H), 7.81-7.66 (m, 6 H), 7.49-7.37 (m, 10

H), 7.34-7.26 (m, 7 H), 3.87-3.70 (m, 3 H), 3.43 (dd, 1 H, *J* = 8.7, 5.7 Hz), 1.59 (dq, 1 H, *J* = 13.5, 6.8 Hz), 1.39 (dq, 1 H, *J* = 13.7, 6.8 Hz), 1.08 (s, 9 H), 1.08-1.01 (m, 1 H), 0.87-0.76 (m, 1 H), 0.44 (dt, 1 H, *J* = 8.6, 4.9 Hz), 0.30 (dt, 1 H, *J* = 8.4, 5.1 Hz); ^{13}C NMR δ 143.22, 143.15, 135.50, 135.47, 134.11, 133.93, 133.89, 133.05, 132.38, 132.25, 131.88, 131.75, 131.65, 131.62, 131.52, 131.49, 131.33, 129.45, 128.40, 128.20, 128.04, 127.53, 127.50, 126.94, 126.70, 63.98, 58.54, 36.40, 26.83, 26.57, 26.51, 19.07, 15.53, 10.20; EIMS *m/z* 629 (M^+, 3), 573 (100), 398 (28), 319 (17), 306 (92), 256 (17), 218 (18), 201 (94), 183 (20); HRMS (EI) *m/z* calcd for $C_{40}H_{44}NO_2PSi$ 629.2879, found 629.2887.



260

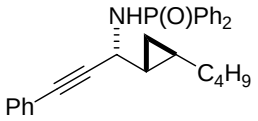
***O*-Triisopropylsilyl-4-[(1*R**,2*R**)-2-{(*R**)-[(diphenylphosphinyl)amino](phenyl)-methyl}cyclopropyl]propanoate (260).** According to the General Protocol C, 390 mg (1.51 mmol) of Cp_2ZrHCl, 426 mg (1.65 mmol) of alkyne **150**, 750 μL (1.50 mmol) of Me_2Zn (2.0 M solution in toluene), 153 mg (0.501 mmol) of imine **104** (4 h reaction time), and 200 μL (2.48 mmol) of CH_2I_2 (16 h reaction time) afforded 205 mg (71%) of **260** as a colorless oil: IR (neat) 3183, 2947, 2866, 1716, 1462, 1437, 1186, 1125, 1111 cm^{-1}; ^{1}H NMR δ 7.94-7.87 (m, 2 H), 7.76-7.69 (m, 2 H), 7.52-7.37 (m, 4 H), 7.32-7.19 (m, 7 H), 3.79 (q, 1 H, *J* = 9.0 Hz), 3.50 (dd, 1 H, *J* = 8.8, 6.1 Hz), 2.46-2.31 (m, 2 H), 1.59 (dq, 1 H, *J* = 14.5, 7.1 Hz), 1.48-1.17 (m, 5 H), 1.06 (d, 18 H, *J* = 7.2 Hz), 0.87-0.75 (m, 1 H), 0.44 (dt, 1 H, *J* = 8.6, 4.9 Hz), 0.30 (dt, 1 H, *J* = 8.4, 5.1 Hz); ^{13}C NMR δ 173.61, 143.12, 134.35, 133.19, 132.44, 132.31, 131.91, 131.79, 128.47, 128.29, 128.10, 127.04, 126.73, 58.59, 35.74, 29.12, 26.91, 18.27, 17.75, 11.88, 10.57; EIMS *m/z* 575 (M^+, 1), 532 (21), 330 (32), 319 (20), 306 (50), 256 (19), 218 (27), 201 (100), 143 (20), 115 (21), 103 (23), 91 (23); HRMS (EI) *m/z* calcd for $C_{34}H_{46}NO_3PSi$ 575.2985, found 575.2979.



261

***O*-Ethyl-*N*-{2-[(1*S**,2*R**)-2-{(*R**)-[(diphenylphosphinyl)amino](phenyl)methyl}-cyclopropyl]ethyl}-*N*-[(4-methylphenyl)sulfonyl]carbamate (261).** According to the General Protocol C, 390 mg (1.51 mmol) of Cp_2ZrHCl, 495 mg (1.68 mmol) of alkyne **152**, 750 μL (1.50 mmol) of Me_2Zn (2.0 M solution in toluene), 153 mg (0.501 mmol) of imine **104** (2 h reaction

time), and 200 μL (2.48 mmol) of CH_2I_2 (12 h reaction time) afforded 138 mg (45%) of **261** as a colorless oil: IR (neat) 3344, 3187, 3060, 2990, 1731, 1438, 1370, 1353, 1274, 1187, 1170, 1123, 1089, 728, 700, 675 cm^{-1}; ^1H NMR δ 7.98-7.91 (m, 2 H), 7.83-7.74 (m, 4 H), 7.53-7.42 (m, 4 H), 7.38-7.25 (m, 9 H), 4.11 (q, 2 H, *J* = 7.1 Hz), 3.90 (t, 2 H, *J* = 7.7 Hz), 3.85-3.72 (m, 1 H), 3.51 (dd, 1 H, *J* = 8.5, 6.3 Hz), 2.46 (s, 3 H), 1.77 (dq, *1* H, J = 13.7, 6.9 Hz), 1.53 (dq, 1 H, *J* = 13.7, 7.7 Hz), 1.20-1.11 (m, 1 H), 1.17 (t, 3 H, *J* = 7.1 Hz), 0.82-0.71 (m, 1 H), 0.47 (dt, 1 H, *J* = 8.6, 5.2 Hz), 0.39 (dt, 1 H, *J* = 8.4, 5.1 Hz); ^{13}C NMR δ 152.22, 144.31, 143.05, 142.98, 136.75, 134.18, 133.01, 132.39, 132.27, 131.93, 131.80, 131.63, 131.60, 131.29, 129.21, 128.51, 128.32, 128.22, 128.15, 127.97, 127.46, 127.09, 126.75, 63.15, 58.61, 46.96, 34.06, 26.53, 26.47, 21.58, 16.11, 13.96, 10.39; EIMS *m/z* 616 (M^+, 2), 461 (8), 415 (10), 360 (9), 319 (17), 306 (100), 256 (15), 243 (24), 216 (23), 201 (89), 155 (39), 91 (52), 77 (28); HRMS (EI) *m/z* calcd for $C_{34}H_{37}N_2O_5PS$ 616.2161, found 616.2154. Approximately 2.5 mg of racemic **261** was separated by HPLC on a Chiracel OD analytical column (solvent system: 7.5% *i*-PrOH in hexanes; flow rate: 1 mL/min). Enantiomer 1: R_T 11.2 min; >99% ee (HPLC chiracel OD analytical column, 7.5% *i*-PrOH in hexanes, 1.0 mL/min); α_D -10.9 ($CHCl_3$, c = 0.1). Enantiomer 2: R_T 16.8 min; >99% ee (HPLC chiracel OD analytical column, 7.5% *i*-PrOH in hexanes, 1.0 mL/min); α_D +11.1 ($CHCl_3$, c = 0.1).

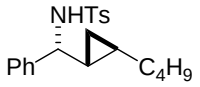


262

***N*-{1-(*R**)-[(1*R**,2*R**)-2-Butylcyclopropyl]-3-phenylprop-2-ynyl}-*P*,*P*-diphenyl-phosphinamide (262).** According to the General Protocol C, 395 mg (1.53 mmol) of Cp_2ZrHCl, 195 μL (1.70 mmol) of 1-hexyne, 750 μL (1.50 mmol) of Me_2Zn (2.0 M solution in toluene), 168 mg (0.510 mmol) of imine **164** (3 h reaction time), and 200 μL (2.48 mmol) of CH_2I_2 (4 h reaction time) afforded 131 mg (60%) of **262** as a colorless oil: IR (neat) 3166, 3058, 2955, 2924, 2855, 1490, 1438, 1189, 1124, 1110, 1070, 755, 723, 692 cm^{-1}; ^1H NMR (600 MHz) δ 8.04-8.00 (m, 2 H), 7.91-7.87 (m, 2 H), 7.52-7.41 (m, 6 H), 7.34-7.28 (m, 5 H), 4.24 (td, 1 H, *J* = 9.4, 5.6 Hz), 3.30 (t, 1 H, *J* = 8.8 Hz), 1.33-1.18 (m, 6 H), 1.11 (dq, 1 H, *J* = 9.9, 5.0 Hz), 0.90-0.84 (m, 1 H), 0.85 (t, 3 H, *J* = 7.1 Hz), 0.69 (dt, 1 H, *J* = 9.0, 4.6 Hz), 0.31 (dt, 1 H, *J* = 8.2, 4.9 Hz); ^{13}C NMR (151 MHz) δ 133.38, 132.77, 132.71, 132.54, 132.38, 131.91, 131.78, 131.72, 131.65, 131.50,

128.52, 128.44, 128.19, 122.78, 87.91, 87.86, 83.84, 46.40, 32.94, 31.64, 24.97, 22.48, 17.58, 14.08, 8.79; EIMS *m/z* 427 (M^+, 2), 370 (9), 330 (16), 201 (100); HRMS (EI) *m/z* calcd for $C_{28}H_{30}NOP$ 427.2065, found 427.2063.

Conversion of 262 to 264. A solution of 50.0 mg (0.117 mmol) of cyclopropane **262** in 5 mL of EtOH was treated with 8.0 mg of 10% Pd on activated charcoal, stirred under an H_2 atmosphere (1 atm) for 16 h, diluted with Et_2O, filtered through Celite and concentrated *in vacuo*. A solution of the residue in 5 mL of a 1 N solution of HCl(g) in MeOH was stirred at room temperature for 4 h, basified with 5% NaOH, and extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$), concentrated *in vacuo*, dissolved in 2 mL of CH_2Cl_2, and treated with 65.0 mg (0.341 mmol) of TsCl, 10.0 mg (0.0819 mmol) of DMAP, and 60.0 μL (0.619 mmol) of Et_3N. The mixture was stirred at room temperature for 16 h, diluted with Et_2O, washed with H_2O and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (9:1, hexanes/EtOAc) to yield 31 mg (68%) of **264** as a colorless oil.

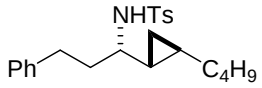


263

***N*-{(*R**)-[(1*R**,2*R**)-2-Butylcyclopropyl]phenylmethyl}-*S*-(4-methylphenyl)sulfonamide (263).** According to the General Protocol C, 193 mg (0.748 mmol) of Cp_2ZrHCl, 95.0 μL (0.827 mmol) of 1-hexyne, 380 μL (0.760 mmol) of Me_2Zn (2.0 M solution in toluene), 64.0 mg (0.247 mmol) of imine **90** (1 h reaction time), and 100 μL (1.24 mmol) of CH_2I_2 (12 h reaction time) afforded 58 mg (66%) of **263** [*dr* = 96:4 (^{1}H NMR)] as a colorless oil: IR (neat) 3277, 2956, 2925, 2856, 1455, 1435, 1326, 1161, 1095, 1056, 1022, 813, 700, 668 cm^{-1}; ^{1}H NMR δ 7.58-7.54 (m, 2 H), 7.17-7.08 (m, 7 H), 5.23 (d, 1 H, *J* = 6.3 Hz), 3.71 (dd, 1 H, *J* = 8.6, 6.3 Hz), 2.35 (s, 3 H), 1.25-1.13 (m, 5 H), 1.07-0.97 (m, 1 H), 0.88-0.77 (m, 1 H), 0.86 (t, 3 H, *J* = 7.1 Hz), 0.57-0.46 (m, 1 H), 0.39 (dt, 1 H, *J* = 8.6, 4.8 Hz), 0.23 (dt, 1 H, *J* = 8.4, 5.0 Hz); ^{13}C NMR δ 142.87, 140.62, 137.76, 129.22, 128.16, 127.16, 127.02, 126.73, 62.07, 33.05, 31.52, 25.36, 22.42, 21.39, 18.53, 14.02, 10.95; CIMS *m/z* 358 ($[M+H]^+$, 37), 273 (15), 260 (50), 187 (100), 173 (39), 117 (37), 105 (24), 91 (39); HRMS (CI) *m/z* calcd for $C_{21}H_{28}NO_2S$ [M+H] 358.1841, found 358.1856.

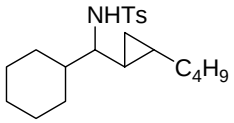
Conversion of 257 to 263. A solution of 88.0 mg (0.218 mmol) of cyclopropane **257** in 5 mL of a 1 N solution of HCl(g) in MeOH (prepared by treating 4.5 mL of MeOH with 0.5 mL

of AcCl at 0 °C and stirring at room temperature for 30 min) was stirred at room temperature for 4 h, basified with 5% NaOH, and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in 2 mL of CH_2Cl_2, and treated with 166 mg (0.871 mmol) of TsCl, 10.0 mg (0.0819 mmol) of DMAP, and 130 μL (1.34 mmol) of Et_3N. The mixture was stirred at room temperature for 16 h, diluted with Et_2O, washed with H_2O and brine, dried ($MgSO_4$), filtered through a pad of Florisil, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (4:1, hexanes/EtOAc) to yield 56 mg (72%) of **263** as a colorless oil.



264

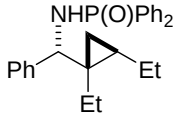
***N*-{1-(*S**)-[(1*R**,2*R**)-2-Butylcyclopropyl]-3-phenylpropyl}-*S*-(4-methylphenyl)-sulfonamide (264).** According to the General Protocol C, 392 mg (1.52 mmol) of Cp_2ZrHCl, 190 μL (1.65 mmol) of 1-hexyne, 750 μL (1.50 mmol) of Me_2Zn (2.0 M solution in toluene), 144 mg (0.501 mmol) of imine **166** (1.5 h reaction time), and 400 μL (4.96 mmol) of CH_2I_2 (17 h reaction time) afforded 130 mg (67%) of **264** [*dr* = 87:13 (^{1}H NMR)] as a colorless oil: IR (neat) 3278, 2954, 2925, 2857, 1454, 1325, 1160, 1095, 814, 700, 665 cm^{-1}; ^{1}H NMR δ 7.76-7.74 (m, 2 H), 7.28-7.15 (m, 5 H), 7.09-7.06 (m, 2 H), 4.84 (d, 1 H, *J* = 7.3 Hz), 2.66-2.60 (m, 3 H), 2.41 (s, 3 H), 1.86-1.76 (m, 2 H), 1.23-1.01 (m, 5 H), 0.94-0.78 (m, 1 H), 0.84 (t, 3 H, *J* = 6.9 Hz), 0.55-0.46 (m, 1 H), 0.30-0.16 (m, 3 H); ^{13}C NMR δ 143.04, 141.65, 138.38, 129.53, 128.26 (2 C), 127.00, 125.73, 58.25, 37.55, 33.18, 31.56, 31.50, 23.64, 22.41, 21.43, 17.41, 14.03, 11.29; CIMS *m/z* 386 ([M+H]$^+$, 76), 288 (61), 280 (32), 215 (74), 172 (81), 131 (67), 119 (48), 117 (100), 105 (36), 91 (82); HRMS (CI) *m/z* calcd for $C_{23}H_{32}NO_2S$ [M+H] 386.2154, found 386.2161.



265

***N*-[(2-Butylcyclopropyl)cyclohexylmethyl]-*S*-(4-methylphenyl)sulfonamide (265).** A suspension of 195 mg (0.756 mmol) of Cp_2ZrHCl in 2 mL of CH_2Cl_2 was treated at room temperature with 100 μL (0.870 mmol) of 1-hexyne. After 10 min, the yellow solution was cooled to -78 °C, treated with 380 μL (0.760 mmol) of Me_2Zn (2.0 M solution in toluene), warmed to room temperature and cannulated into a solution of 66.0 mg (0.249 mmol) of imine

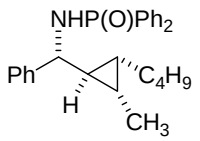
170 in 1 mL of CH_2Cl_2. The mixture was heated at reflux for 2 h, cooled to 0 °C, treated with 200 μL (2.48 mmol) of CH_2I_2 and 380 μL (0.760 mmol) of Me_2Zn (2.0 M solution in toluene), heated at reflux for 12 h, cooled to room temperature, quenched with saturated $NaHCO_3$, diltued with EtOAc, filtered through Celite, washed with H_2O and brine, dried ($MgSO_4$), filtered through a pad of Florisil and concentrated *in vacuo*. The residue was purified on SiO_2 (80:20, hexanes/EtOAc) to yield 66 mg of a 85:15 mixture of **265** (major isomer: 37%, minor isomer: 25%) to **171** (11%). **265** (major isomer, colorless oil): IR (neat) 3281, 2924, 2843, 1445, 1327, 1161, 1088, 1015 cm^{-1}; ^1H NMR δ 7.73 (d, 2 H, *J* = 8.3 Hz), 7.25 (d, 2 H, *J* = 8.0 Hz), 4.88 (d, 1 H, *J* = 7.6 Hz), 2.43-2.36 (m, 1 H), 2.40 (s, 3 H), 1.69-1.37 (m, 6 H), 1.23-0.92 (m, 11 H), 0.82 (t, 3 H, *J* = 6.7 Hz), 0.51-0.40 (m, 2 H), -0.08 (dt, 1 H, *J* = 7.7, 5.2 Hz), -0.16 (dt, 1 H, *J* = 8.4, 4.9 Hz); ^{13}C NMR δ 142.79, 138.77, 129.32, 127.01, 63.54, 43.39, 33.29, 31.34, 28.93, 28.70, 26.42, 26.37, 26.22, 22.44, 21.45, 21.20, 18.77, 13.99, 10.27; CIMS *m/z* 364 ($[M+H]^+$, 22), 266 (100), 193 (27); HRMS (CI) *m/z* calcd for $C_{21}H_{34}NO_2S$ [M+H] 364.2310, found 364.2321.



266

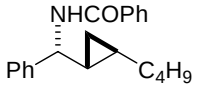
***N*-{(*R**)-[(1*R**,2*R**)-1,2-Diethylcyclopropyl](phenyl)methyl}-*P*,*P*-diphenylphosphinamide (266).** According to the General Protocol C, 390 mg (1.51 mmol) of Cp_2ZrHCl, 190 μL (1.67 mmol) of 3-hexyne, 750 μL (1.50 mmol) of Me_2Zn (2.0 M solution in toluene), 153 mg (0.501 mmol) of imine **104** (3 h reaction time), and 200 μL (2.48 mmol) CH_2I_2 (12 h reaction time) afforded 93 mg (46%) of **266** [*dr* = 96:4 (HPLC)] as a colorless solid: mp 136-137 °C (EtOAc/hexane); IR (KBr) 3188, 3058, 2961, 2930, 2870, 1453, 1426, 1185, 1123, 1109, 1094, 1063, 752, 720, 699 cm^{-1}; ^1H NMR δ 7.91-7.84 (m, 2 H), 7.76-7.68 (m, 2 H), 7.55-7.40 (m, 4 H), 7.34-7.21 (m, 5 H), 7.19-7.16 (m, 2 H), 4.24 (t, 1 H, *J* = 10.7 Hz), 3.23 (dd, 1 H, *J* = 10.0, 7.0 Hz), 1.69 (dq, 1 H, *J* = 14.8, 7.4 Hz), 1.50 (dq, 1 H, *J* = 13.9, 6.9 Hz), 1.31-1.16 (m, 2 H), 0.97-0.84 (m, 1 H), 0.94 (t, 3 H, *J* = 7.3 Hz), 0.87 (t, 3 H, *J* = 7.3 Hz), 0.66 (tt, 1 H, *J* = 8.5, 6.1 Hz), -0.03 (dd, 1 H, *J* = 5.5, 4.8 Hz); ^{13}C NMR δ 142.31, 142.25, 134.18, 132.79, 132.60, 132.47, 131.92, 131.79, 131.72, 131.69, 131.57, 131.53, 131.06, 128.47, 128.31, 128.15, 127.99, 127.20, 126.81, 58.08, 30.69, 30.62, 23.69, 22.92, 21.95, 14.36, 14.07, 11.57; EIMS *m/z* 403 (M^+, 7), 306

(46), 284 (59), 218 (45), 201 (100), 157 (17), 146 (15), 129 (19), 91 (10), 77 (16); HRMS (EI) *m/z* calcd for $C_{26}H_{30}NOP$ 403.2065, found 403.2075.



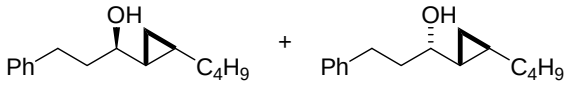
267

***N*-(*R**)-{[(1*R**,2*R**,3*R**)-2-Butyl-3-methylcyclopropyl]phenylmethyl}-*P*,*P*-diphenylphosphinamide (267).** A suspension of 195 mg (0.756 mmol) of Cp_2ZrHCl in 2 mL of THF was treated at room temperature with 100 μL (0.870 mmol) of 1-hexyne, stirred for 10 min and concentrated *in vacuo*. A solution of the resulting yellow solid in 2 mL of $(CH_2Cl)_2$ was cooled to -78 °C, treated with 380 μL (0.760 mmol) of Me_2Zn (2.0 M solution in toluene), warmed to room temperature and cannulated into a suspension of 76.0 mg (0.249 mmol) of imine **104** in 1 mL of $(CH_2Cl)_2$. The mixture was stirred for 2 h at 40 °C, cooled to -78 °C, treated with 680 μL (0.748 mmol) of Et_2Zn (1.1 M solution in toluene) and 130 μL (1.29 mmol) of CH_3CHI_2, stirred for 16 h at 40 °C, cooled to room temperature, treated with a cold (0 °C) solution of 680 μL (0.748 mmol) of Et_2Zn (1.1 M solution in toluene), 130 μL (1.29 mmol) of CH_3CHI_2, and 80.0 μL (0.770 mmol) of DME in 1 mL of $ClCH_2CH_2Cl$, and stirred for 24 h at 40 °C, quenched with saturated $NaHCO_3$, diluted with EtOAc, filtered through Celite, washed with H_2O and brine, dried ($MgSO_4$), filtered through a pad of Florisil, and concentrated *in vacuo*. The residue was chromatographed on deactivated SiO_2 (1:4, hexanes/EtOAc containing 1% Et_3N) to yield 20 mg (21%) of **146** and 54 mg (52%) of **267** as colorless solids. **267**: mp 152-153 °C (Et_2O/hexane); IR (KBr) 3200, 2955, 2923, 2861, 1435, 1185, 1123, 1107, 1067, 749, 726, 698 cm^{-1}; ^1H NMR δ 7.92-7.85 (m, 2 H), 7.77-7.70 (m, 2 H), 7.49-7.40 (m, 4 H), 7.38-7.22 (m, 9 H), 3.76 (q, 1 H, *J* = 8.9 Hz), 3.25 (bt, 1 H, *J* = 7.1 Hz), 1.31-1.18 (m, 6 H), 0.92-0.84 (m, 6 H), 0.70-0.67 (m, 2 H), 0.61 (dt, 1 H, *J* = 8.0, 4.7 Hz); ^{13}C NMR δ 143.76, 143.70, 133.18, 132.58, 132.45, 132.33, 132.03, 131.90, 131.73, 131.69, 131.60, 131.57, 128.47, 128.30, 128.23, 128.12, 126.87, 126.74, 58.92, 34.06, 33.99, 32.32, 27.49, 23.13, 22.73, 15.95, 14.17, 12.33; EIMS *m/z* 417 (M^+, 2), 306 (100), 201 (56), 106 (19); HRMS (EI) *m/z* calcd for $C_{27}H_{32}NOP$ 417.2222, found 417.2237.



268

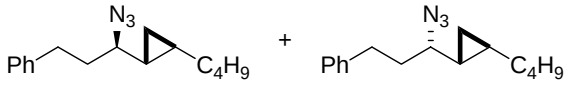
***N*-{(*R**)-[(1*R**,2*R**)-2-Butylcyclopropyl](phenyl)methyl}benzamide (268).** A solution of 91.0 mg (0.226 mmol) of **257** in 5 mL of a 1 N solution of HCl(g) in MeOH was stirred at room temperature for 3 h, basified with 5% NaOH, and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), concentrated *in vacuo*, dissolved in 3 mL of CH_2Cl_2, and treated with 205 mg (0.906 mmol) of $(PhCO)_2O$, 10.0 mg (0.0819 mmol) of DMAP, and 240 μL (1.38 mmol) of $(i\text{-Pr})_2NEt$. The mixture was stirred at room temperature for 1 h, poured into EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (80:20, hexanes/EtOAc) to yield 69 mg (99%) of **268** as a colorless solid: mp 115-116 °C (hexane); IR (KBr) 3354, 2955, 2921, 2954, 1632, 1524, 1490, 701 cm^{-1}; ^1H NMR δ 7.85-7.81 (m, 2 H), 7.57-7.28 (m, 8 H), 6.54 (d, 1 H, *J* = 7.9 Hz), 4.72 (t, 1 H, *J* = 8.3 Hz), 1.44-1.32 (m, 5 H), 1.25-1.20 (m, 1 H), 1.05-0.98 (m, 2 H), 0.88 (t, 3 H, *J* = 7.1 Hz), 0.65 (dt, 1 H, *J* = 8.2, 4.9 Hz), 0.49 (dt, 1 H, *J* = 8.0, 5.3 Hz); ^{13}C NMR δ 166.60, 141.99, 134.67, 131.41, 128.54, 128.47, 127.24, 126.88, 126.67, 57.15, 33.42, 31.86, 24.31, 22.42, 17.87, 14.05, 11.38; EIMS *m/z* 307 (M^+, 19), 292 (4), 264 (6) 250 (14), 236 (16), 222 (31), 210 (40), 160 (15), 152 (22), 105 (100), 77 (53); HRMS (EI) *m/z* calcd for $C_{21}H_{25}NO$ 307.1936, found 307.1935.



syn-**271** *anti*-**271**

1-(*R)-[(1*R**,2*R**)-2-Butylcyclopropyl]-3-phenylpropan-1-ol (*syn*-271)** and **1-(*S**)-[(1*R**,2*R**)-2-butylcyclopropyl]-3-phenylpropan-1-ol (*anti*-271).** A solution of 361 mg (1.65 mmol) of 1-phenylnon-4-en-3-ol (**270**) in 15 mL of CH_2Cl_2 was treated at room temperature with 530 μL (6.58 mmol) of CH_2I_2, cooled to 0 °C, treated with 3.40 mL (3.40 mmol) of Et_2Zn (1.0 M solution in hexanes), stirred at room temperature for 12 h, quenched with saturated NH_4Cl, diluted with EtOAc and saturated $NaHCO_3$, filtered through Celite, washed with H_2O and brine, dried ($MgSO_4$), filtered through a pad of Florisil, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (4:1, hexanes/EtOAc) to yield 47 mg (12%) of *anti*-**271** and 300 mg (78%) of *syn*-**271** as colorless oils. *anti*-**271**: IR (neat) 3394, 3062, 3026, 2992, 2855, 1716, 1602, 1496, 1454, 1046 cm^{-1}; ^1H NMR δ 7.47-7.30 (m, 5 H), 3.10 (q, 1 H, *J* = 6.8

Hz), 3.02-2.82 (m, 2 H), 2.08-2.01 (m, 2 H), 1.68 (s, 1 H), 1.58-1.31 (m, 6 H), 1.05 (t, 3 H, J = 7.0 Hz), 0.88-0.76 (m, 2 H), 0.54-0.44 (m, 2 H); ^{13}C NMR δ 142.28, 128.36, 128.30, 125.68, 75.57, 38.54, 33.37, 32.03, 31.92, 25.57, 22.50, 16.81, 14.07, 9.92; EIMS *m/z* 232 (M^+, 7), 215 (7), 148 (15), 130 (51), 109 (28), 105 (29), 91 (100); HRMS (EI) *m/z* calcd for $C_{16}H_{24}O$ 232.1827, found 232.1824. *syn*-**271**: IR (neat) 3391 3026, 2919, 2855, 1496, 1454, 1031 cm^{-1}; ^{1}H NMR δ 7.47-7.31 (m, 5 H), 3.10-2.82 (m, 3 H), 2.11-2.04 (m, 2 H), 1.71 (s, 1 H), 1.53-1.35 (m, 6 H), 1.05 (t, 3 H, J = 7.0 Hz), 0.88-0.80 (m, 1 H), 0.78-0.69 (m, 1 H), 0.58 (dt, 1 H, J = 8.8, 4.4 Hz), 0.45 (dt, 1 H, J = 8.0, 4.7 Hz); ^{13}C NMR δ 142.27, 128.36, 128.33, 125.71, 75.67, 38.75, 33.32, 32.01, 31.66, 25.76, 2250, 17.01, 14.05, 9.97; EIMS *m/z* 232 (M^+, 2), 214 (6), 130 (25), 109 (20), 109 (20), 91 (86); HRMS (EI) *m/z* calcd for $C_{16}H_{24}O$ 232.1827, found 232.1827.



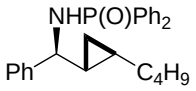
syn-**272** *anti*-**272**

3-(*S)-Azido-3-[(1*R**,2*R**)-2-butylcyclopropyl]propylbenzene (*anti*-272)** and **3-(*S**)-Azido-3-[(1*R**,2*R**)-2-butylcyclopropyl]propylbenzene (*syn*-272).** According to a literature procedure, a solution of 68.0 mg (0.293 mmol) of *syn*-**271** in 3 mL of THF was treated with 55.0 μL (0.349 mmol) of DEAD, 76.0 μL (0.352 mmol) of diphenylphosphoryl azide and 92.0 mg (0.351 mmol) of PPh_3, stirred at room temperature for 16 h, diluted with Et_2O, filtered through a pad of Florisil, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (9:1, hexanes/EtOAc) to yield 64 mg (85%) of **272** as an (inseparable) 78:22 (*anti*: *syn*) mixture of diastereomers: IR (neat) 3027, 2998, 2922, 2856, 2097, 1496, 1454, 1248, 1031 cm^{-1}; ^{1}H NMR δ 7.34-7.28 (m, 2 H), 7.23-7.19 (m, 3 H), 2.86-2.63 (m, 3 H), 1.96-1.85 (m, 2 H), 1.49-1.19 (m, 6 H), 0.93 (t, 3 H, J = 7.1 Hz), 0.87-0.73 (m, 1.78 H), 0.64-0.54 (m, 0.44 H), 0.54-0.43 (m, 0.22 H), 0.41-0.32 (m, 1.56 H); ^{13}C NMR (major isomer) δ 141.39, 128.39, 128.33, 125.91, 66.54, 36.42, 33.36, 32.28, 31.30, 22.70, 22.46, 17.80, 13.99, 10.04; EIMS *m/z* 230 ([M-N_2+H]$^+$, 56), 215 (100), 186 (23), 172 (50), 158 (47), 144 (48), 131 (42), 117 (86), 106 (38); HRMS (EI) *m/z* calcd for $C_{16}H_{23}N$ [M-N_2] 229.1831, found 229.1834.

According to a literature procedure, a solution of 76.0 mg (0.327 mmol) of *anti*-**271** in 3 mL of THF was treated with 62.0 μL (0.394 mmol) of DEAD, 85.0 μL (0.422 mmol) of diphenylphosphoryl azide and 103 mg (0.393 mmol) of PPh_3, stirred at room temperature for 16 h, diluted with Et_2O, filtered through a pad of SiO_2, and concentrated *in vacuo*. The residue was

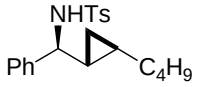
chromatographed on SiO_2 (50:1, hexanes/EtOAc) to yield 49 mg (58%) of **272** as an (inseparable) 15:85 (*anti*:*syn*) mixture of diastereomers.

Conversion of *anti*-272 into 264. A solution of 77.0 mg (0.299 mmol) of a 78:22 (*anti*:*syn*) mixture of **272** in 2 mL of THF was treated with 12.0 mg of 10% Pd on activated charcoal, stirred under an H_2 atmosphere (1 atm) for 12 h, filtered through Celite, and concentrated *in vacuo*. A solution of the residue in 3 mL of CH_2Cl_2 was treated with 228 mg (1.20 mmol) of TsCl 10.0 mg (0.0819 mmol) of DMAP, and 170 μL (1.75 mmol) of Et_3N, stirred at room temperature for 16 h, diluted with Et_2O, washed with H_2O and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (4:1, hexanes/ EtOAc) to yield 76 mg (66%) of **264** as a colorless oil.



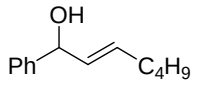
syn-**257**

Preparation of 257 by Simmons-Smith Cyclopropanation of Allylic Amide 146. *N*-{(*S)-[(1*R**,2*R**)-2-Butylcyclopropyl](phenyl)methyl}-*P*,*P*-diphenylphosphinamide (*syn*-257).** A solution of 1.50 mL (1.50 mmol) of Et_2Zn (1.0 M solution in hexanes) in 4 mL of CH_2Cl_2 was cooled to 0 °C and treated with 250 μL (310 mmol) of CH_2I_2 and a solution of 289 mg (0.742 mmol) of phosphinamide **146** in 4 mL of CH_2Cl_2, stirred at room temperature for 16 h, quenched with saturated NH_4Cl, diluted with EtOAc and saturated $NaHCO_3$, filtered through Celite, washed with brine, dried ($MgSO_4$), filtered through a pad of Florisil, and concentrated *in vacuo*. The residue was chromatographed on deactivated SiO_2 (1:4, hexanes/EtOAc, containing 1% Et_3N) to yield 242 mg (81%) of **257** as a 71:29 (*anti*:*syn*) mixture of diastereoisomers. *syn*-**257** (colorless solid): mp 142-143 °C (EtOAc/hexanes); IR (thin film) 3179, 2959, 2918, 2850, 1437, 1183, 1124, 725, 696 cm^{-1}; ^1H NMR δ 7.96-7.90 (m, 2 H), 7.78-7.72 (m, 2 H), 7.53-7.39 (m, 4 H), 7.34-7.22 (m, 7 H), 3.65 (t, 1 H, *J* = 9.2 Hz), 3.31 (bs, 1 H), 1.10-0.97 (m, 6 H), 0.96-0.88 (m, 1 H), 0.73 (t, 3 H, *J* = 6.6 Hz), 0.60-0.53 (m, 2 H), 0.32-0.27 (m, 1 H); ^{13}C NMR δ 132.42, 132.29, 132.10, 131.98, 131.71, 131.56, 128.44, 128.28, 128.13, 127.01, 126.69, 59.67, 33.15, 31.38, 27.16, 22.18, 18.14, 13.87, 12.64; ESIMS *m/z* 426 ($[M+Na]^+$, 100), 404 ($[M+H]^+$, 45); HRMS (ESI) *m/z* calcd for $C_{26}H_{30}NOPNa$ 426.1963, found 426.1947.



syn-**263**

Preparation of 263 by Simmons-Smith Cyclopropanation of Allylic Amide 91. *N*-{(*S)-[(1*R**,2*R**)-2-Butylcyclopropyl]phenylmethyl}-*S*-(4-methylphenyl)sulfonamide (*syn*-263).** A solution of 1.50 mL (1.50 mmol) of Et_2Zn (1.0 M solution in hexanes) in 4 mL of CH_2Cl_2 was cooled to 0 °C and treated with 250 μL (310 mmol) of CH_2I_2 and a solution of 238 mg (0.693 mmol) of sulfonamide **91** in 4 mL of CH_2Cl_2, stirred at room temperature for 16 h, quenched with saturated NH_4Cl, diluted with EtOAc and saturated $NaHCO_3$, filtered through Celite, washed with brine, dried ($MgSO_4$), filtered through a pad of Florisil, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (4:1, hexanes/ EtOAc) to yield 231 mg (93%) of **263** as a 81:19 (*anti*:*syn*) mixture of diastereoisomers. *syn*-**263**: IR (thin film) 3277, 2957, 2920, 2852, 1432, 1324, 1160, 1050, 812, 699, 666 cm^{-1}; ^1H NMR δ 7.56-7.51 (m, 2 H), 7.17-7.07 (m, 7 H), 5.06 (d, 1 H, *J* = 5.6 Hz), 3.66 (dd, 1 H, *J* = 8.8, 5.7 Hz), 2.35 (s, 3 H), 1.13-0.97 (m, 6 H), 0.80-0.73 (m, 1 H), 0.70 (t, 3 H, *J* = 6.9 Hz), 0.63-0.60 (m, 1 H), 0.35 (dt, 1 H, *J* = 8.6, 4.9 Hz), 0.26 (dt, 1 H, *J* = 8.0, 5.1 Hz); ^{13}C NMR δ 142.91, 140.73, 137.66, 129.20, 128.17, 127.21, 127.11, 126.67, 62.33, 32.95, 31.24, 25.74, 22.12, 21.44, 18.01, 13.92, 11.65; EIMS *m/z* 357 (M^+, 1), 273 (53), 260 (38), 160 (49), 155 (46), 129 (22), 118 (63), 104 (37), 91 (100); HRMS (EI) *m/z* calcd for $C_{21}H_{27}NO_2S$ 357.1763, found 357.1751.

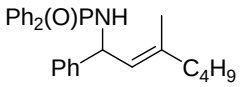


33

Attempted preparation of (2-butylcyclopropyl)phenylmethanol. (*E*)-1-Phenylhept-2-en-1-ol (33). A suspension of 390 mg (1.51 mmol) of Cp_2ZrHCl in 3 mL of CH_2Cl_2 was treated at room temperature with 190 μL (1.65 mmol) of 1-hexyne. After 5 min, the yellow solution was cooled to -78 °C, treated with 750 μL (1.50 mmol) of Me_2Zn (2.0 M solution in toluene), warmed to room temperature over a period of 5 min, treated with 50.0 μL (0.492 mmol) of PhCHO, heated at reflux for 48 h, quenched with saturated NH_4Cl, diluted with EtOAc, filtered through Celite, washed with H_2O and brine, dried ($MgSO_4$), filtered through a pad of Florisil and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (4:1, hexanes/EtOAc) to yield 84 mg (90%) of **33** as a colorless oil: ^1H NMR δ 7.37-7.25 (m, 5 H), 5.77 (dt, 1 H, *J* = 15.4, 6.4

Hz), 5.65 (dd, 1 H, *J* = 15.4, 6.4 Hz), 5.14 (d, 1 H, *J* = 6.3 Hz), 2.15 (s, 1 H), 2.09-2.03 (m, 2 H), 1.43-1.29 (m, 4 H), 0.90 (t, 3 H, *J* = 7.0 Hz).

Attempted preparation of 266 using a B-Zn transmetalation. A solution of 190 μL (1.67 mmol) of 3-hexyne in 2.5 mL of CH_2Cl_2 was cooled to 0 °C, and treated with 500 μL (0.500 mmol) of borane (1.0 M solution in THF). The mixture was stirred at 0 °C for 1 h, treated with 750 μL (1.50 mmol) of Me_2Zn (2.0 M solution in toluene), warmed to room temperature, treated with a solution of 152 mg (0.498 mmol) of imine **104** in 1 mL of CH_2Cl_2, heated at reflux for 16 h, quenched with saturated NH_4Cl, diluted with EtOAc, filtered through Celite, washed with H_2O, saturated $NaHCO_3$ and brine, dried ($MgSO_4$), filtered through a pad of Florisil and concentrated *in vacuo*. The residue was chromatographed on deactivated SiO_2 (1:4, hexanes/ EtOAc containing 1% Et_3N) to yield 96 mg (50%) of **147**.

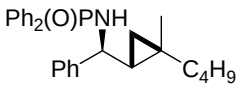


276

Attempted preparation of 278 using an Al-Zn transmetalation. (*E*)-*N*-(3-Methyl-1-phenylhept-2-enyl)-*P*,*P*-diphenylphosphinamide (276). A suspension of 15.0 mg (0.0513 mmol) of Cp_2ZrCl_2 in 5 mL of CH_2Cl_2 was treated at 0 °C with 208 mg (2.89 mmol) of Me_3Al, 27.0 μL (1.50 mmol) of H_2O, and 175 μL (1.52 mmol) of 1-hexyne. The mixture was stirred at 0 °C for 30 min, cooled to -78 °C, treated with 750 μL (1.50 mmol) of Me_2Zn, warmed to room temperature, treated with a solution of 153 mg (0.501 mmol) of imine **104** in 1 mL of CH_2Cl_2, heated at reflux for 12 h, cooled to room temperature, quenched with saturated $NaHCO_3$, diluted with EtOAc, filtered through Celite, washed with 2 N HCl, H_2O and brine, dried ($MgSO_4$), filtered through Florisil, and concentrated *in vacuo*. The residue was chromatographed on deactivated SiO_2 (1:4, hexanes/EtOAc, containing 1% Et_3N) to yield 109 mg (54%) of **276** as a colorless oil: IR (thin film) 3057, 2957, 2927, 1669, 1437, 1185, 1126, 753, 724, 696 cm^{-1}; ^1H NMR δ 7.98-7.91 (m, 2 H), 7.88-7.81 (m, 2 H), 7.50-7.17 (m, 11 H), 5.34 (dd, 1 H, *J* = 9.3, 1.2 Hz), 5.05 (q, 1 H, *J* = 9.0 Hz), 3.25 (t, 1 H, *J* = 7.2 Hz), 1.91 (t, 2 H, *J* = 7.0 Hz), 1.37 (d, 3 H, *J* = 1.3 Hz), 1.35-1.21 (m, 4 H), 0.88 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR δ 143.72, 143.65, 137.41, 133.81, 133.65, 132.55, 132.42, 132.11, 131.92, 131.79, 131.58, 128.43, 128.30, 128.22, 128.13, 126.94, 126.74, 126.21, 126.15, 52.81, 39.12, 30.47, 29.74, 22.40, 16.22, 13.94; EIMS *m/z* 403

(M^+, 1), 346 (1), 306 (2), 216 (82), 201 (35), 199 (66), 140 (46), 124 (58), 105 (46), 77 (100); HRMS (EI) *m/z* calcd for $C_{26}H_{30}NOP$ 403.2065, found 403.2067.

Preparation of 276 using the General Protocol A. A suspension of 15.0 mg (0.0513 mmol) of Cp_2ZrCl_2 in 5 mL of toluene was treated at 0 °C with 210 mg (2.91 mmol) of Me_3Al, 27.0 μL (1.50 mmol) of H_2O, and 175 μL (1.52 mmol) of 1-hexyne. The mixture was stirred at 0 °C for 30 min, treated with 750 μL (1.50 mmol) of Me_2Zn, warmed to room temperature, cannulated into a suspension of 153 mg (0.501 mmol) of imine **104** in 1 mL of toluene, stirred at room temperature for 6 h, quenched with saturated $NaHCO_3$, diluted with EtOAc, filtered through Celite, washed with H_2O and brine, dried ($MgSO_4$), filtered through Florisil, and concentrated *in vacuo*. The residue was chromatographed on deactivated SiO_2 (1:4, hexanes/ EtOAc, containing 1% Et_3N) to yield 147 mg (73%) of **276** as a colorless oil.



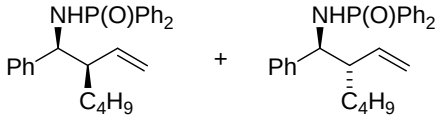
278

***N*-{(*S**)-[(1*R**,2*R**)-2-Butyl-2-methyl-cyclopropyl](phenyl)methyl}-*P*,*P*-diphenyl-phosphinamide (278).** A suspension of 15.0 mg (0.0513 mmol) of Cp_2ZrCl_2 in 5 mL of CH_2Cl_2 was treated at 0 °C with 208 mg (2.89 mmol) of Me_3Al, 27.0 μL (1.50 mmol) of H_2O, and 175 μL (1.52 mmol) of 1-hexyne. The mixture was stirred at 0 °C for 30 min, cooled to -78 °C, treated with 750 μL (1.50 mmol) of Me_2Zn, warmed to room temperature, treated with a solution of 153 mg (0.501 mmol) of imine **104** in 1 mL of CH_2Cl_2, heated at reflux for 4 h, cooled to room temperature, treated with 200 μL (2.48 mmol) of CH_2I_2, heated at reflux for 12 h, cooled to room temperature, quenched with saturated $NaHCO_3$, diluted with EtOAc, filtered through Celite, washed with H_2O and brine, dried ($MgSO_4$), filtered through Florisil, and concentrated *in vacuo*. The residue was chromatographed on deactivated SiO_2 (1:4, hexanes/EtOAc, containing 1% Et_3N) to yield 59 mg (28%) of **278** as an 88:12 (*syn*:*anti*) mixture of diastereomers, and 94 mg (46%) of **276** as a colorless oil. **278** (colorless solid): mp 116-118 °C (EtOAc/hexanes); IR (KBr) 3189, 3059, 2953, 2923, 2871, 1435, 1186, 1124, 1107, 1065, 931, 749, 723, 698 cm^{-1}; ^1H NMR δ 7.93-7.86 (m, 2 H), 7.77-7.69 (m, 2 H), 7.47-7.34 (m, 5 H), 7.31-7.14 (m, 6 H), 3.81 (q, 1 H, *J* = 9.3 Hz), 3.35 (t, 1 H, *J* = 7.8 Hz), 1.25-0.95 (m, 7 H), 0.81 (s, 3 H), 0.73 (t, 3 H, *J* = 6.8 Hz), 0.47 (dd, 1 H, *J* = 8.4, 4.8 Hz), 0.31 (t, 1 H, *J* = 5.1 Hz); ^{13}C NMR δ 144.57, 144.50, 134.35, 133.38, 132.65, 132.24, 132.13, 132.02, 131.56, 131.44, 128.26, 128.13, 128.04, 126.86,

126.70, 56.76, 40.63, 32.10, 28.39, 22.61, 21.79, 19.68, 17.81, 13.94; EIMS *m/z* 417 (M^+, 6), 374 (7), 319 (31), 306 (64), 218 (45), 201 (100), 129 (31), 106 (34), 91 (44), 77 (65); HRMS (EI) *m/z* calcd for $C_{27}H_{32}NOP$ 417.2222, found 417.2222.

Preparation of 278 using a modified General Protocol C (no Al-Zn transmetalation). A suspension of 15.0 mg (0.0513 mmol) of Cp_2ZrCl_2 in 5 mL of toluene was treated at 0 °C with 210 mg (2.91 mmol) of Me_3Al, 27.0 μL (1.50 mmol) of H_2O, and 175 μL (1.52 mmol) of 1-hexyne. The mixture was stirred at 0 °C for 30 min, warmed to room temperature, cannulated into a suspension of 153 mg (0.501 mmol) of imine **104** in 1 mL of toluene, stirred at room temperature for 7 h, and treated with 320 μL (4.05 mmol) of CH_2I_2, stirred at room temperature for 12 h, quenched with saturated $NaHCO_3$, diluted with EtOAc, filtered through Celite, washed with H_2O and brine, dried ($MgSO_4$), filtered through Florisil, and concentrated *in vacuo*. The residue was chromatographed on deactivated SiO_2 (1:4, hexanes/EtOAc, containing 1% Et_3N) to yield 99 mg (47%) of **278** as an 90:10 (*syn*:*anti*) mixture of diastereomers, and 64 mg (32%) of **276** as a colorless oil.

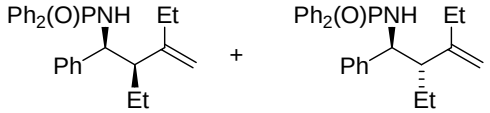
Preparation of 278 by Simmons-Smith Cyclopropanation of Allylic Amide 276. A solution of 147 mg (0.364 mmol) of phosphinamide **276** in 4 mL of CH_2Cl_2 was cooled to 0 °C and treated with 180 μL (2.23 mmol) of CH_2I_2 and 1.00 mL (1.10 mmol) of Et_2Zn (1.1 M solution in toluene), stirred at room temperature for 16 h, quenched with saturated $NaHCO_3$, diluted with EtOAc, filtered through Celite, washed with H_2O and brine, dried ($MgSO_4$), filtered through Florisil, and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (3:7, hexanes/EtOAc) to yield 86 mg (57%) of **278** as a colorless solid, and 21 mg (14%) of phosphinamide **276** was recovered.



syn-**279** *anti*-**279**

***N*-[(1*S**,2*R**)-2-Butyl-1-phenylbut-3-enyl]-*P*,*P*-diphenylphosphinamide (*syn*-279)** and ***N*-[(1*S**,2*S**)-2-butyl-1-phenylbut-3-enyl]-*P*,*P*-diphenylphosphinamide (*anti*-279). General Protocol D.** A suspension of 195 mg (0.756 mmol) of Cp_2ZrHCl in 2 mL of CH_2Cl_2 was treated at room temperature with 95.0 μL (0.827 mmol) of 1-hexyne. After 5 min, the yellow solution was cooled to -78 °C, treated with 560 μL (1.12 mmol) of Me_2Zn (2.0 M solution in toluene), and warmed to room temperature over a period of 5 min. The mixture was

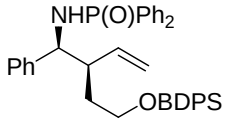
treated with 60.0 μL (0.745 mmol) of CH_2I_2, stirred for 2 min, treated with a solution of 76.0 mg (0.249 mmol) of imine **104** in 1 mL of CH_2Cl_2, stirred at room temperature for 12 h, quenched with saturated NH_4Cl, diluted with EtOAc and saturated $NaHCO_3$, filtered through Celite, washed with H_2O and brine, dried ($MgSO_4$), filtered through a pad of Florisil and concentrated *in vacuo*. The residue was chromatographed on deactivated SiO_2 (1:9, hexanes/EtOAc containing 1% Et_3N) to yield 71 mg (71%) of **279** as an 85:15 mixture of diastereomers. *syn*-**279** (colorless solid): mp 158-159 °C (EtOAc/hexane); IR (KBr) 3221, 3059, 2951, 2914, 2858, 1436, 1185, 1123, 1108, 1068, 919, 723, 702, 692 cm^{-1}; ^1H NMR δ 7.90-7.83 (m, 2 H), 7.73-7.65 (m, 2 H), 7.54-7.38 (m, 4 H), 7.32-7.24 (m, 5 H), 7.07-7.04 (m, 2 H), 5.43 (dt, 1 H, *J* = 17.2, 9.7 Hz), 5.25 (dd, 1 H, *J* = 17.5, 2.2 Hz), 5.21 (dd, 1 H, *J* = 9.8, 2.4 Hz), 4.23 (td, 1 H, *J* = 11.2, 4.6 Hz), 3.75 (dd, 1 H, *J* = 10.8, 6.5 Hz), 2.59 (tt, 1 H, *J* = 10.0, 4.2 Hz), 1.47-1.38 (m, 1 H), 1.33-1.13 (m, 4 H), 1.02-0.86 (m, 1 H), 0.83 (t, 3 H, *J* = 6.7 Hz); ^{13}C NMR δ 140.89, 140.82, 137.80, 134.13, 132.68, 132.61, 132.55, 132.45, 131.76, 131.72, 131.66, 131.57, 131.53, 130.86, 128.51, 128.35, 128.16, 128.00, 127.71, 127.61, 126.85, 119.07, 57.72, 52.11, 52.07, 31.65, 29.57, 22.53, 13.98; EIMS *m/z* 403 (M^+, 1), 306 (100), 201 (98), 77 (22); HRMS (EI) *m/z* calcd for $C_{26}H_{30}NOP$ 403.2065, found 403.2068. *anti*-**279** (colorless solid): mp 160-161 °C (EtOAc/ hexane); IR (KBr) 3181, 2953, 2928, 2852, 1435, 1180, 1126, 1109, 915, 745, 726, 696 cm^{-1}; ^1H NMR δ 7.87-7.80 (m, 2 H), 7.70-7.62 (m, 2 H), 7.54-7.34 (m, 4 H), 7.30-7.19 (m, 5 H), 7.13-7.09 (m, 2 H), 5.72 (ddd, 1 H, *J* = 17.2, 10.3, 8.8 Hz), 5.25 (dd, 1 H, *J* = 10.3, 1.9 Hz), 5.11 (ddd, 1 H, *J* = 17.2, 1.8, 0.7 Hz), 4.14 (dt, 1 H, *J* = 10.1, 7.4 Hz), 3.45 (t, 1 H, *J* = 6.1 Hz), 2.40-2.31 (m, 1 H), 1.35-1.09 (m, 6 H), 0.81 (t, 3 H, *J* = 6.6 Hz); ^{13}C NMR δ 142.78, 142.74, 139.25, 132.72, 132.57, 132.44, 132.34, 131.78, 131.73, 131.70, 131.66, 131.42, 131.39, 130.98, 128.48, 128.32, 128.04, 128.00, 127.87, 127.74, 127.65, 127.28, 126.86, 118.09, 58.13, 51.86, 51.79, 30.31, 29.39, 22.45, 13.97; EIMS *m/z* 404 ($[M+H]^+$, 3), 306 (100), 201 (96), 77 (67); HRMS (EI) *m/z* calcd for $C_{26}H_{31}NOP$ [M+H] 404.2143, found 404.2142.



syn-**280** *anti*-**280**

***N*-[(1*S**,2*R**)-2,3-Diethyl-1-phenylbut-3-enyl]-*P*,*P*-diphenylphosphinamide (*syn*-280)** and ***N*-[(1*S**,2*S**)-2,3-diethyl-1-phenylbut-3-enyl]-*P*,*P*-diphenylphosphinamide (*anti*-280).** According to the General Protocol D, 387 mg (1.50 mmol) of Cp_2ZrHCl, 190 μL (1.65 mmol) of

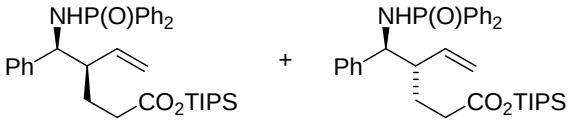
3-hexyne, 1.25 mL (2.50 mmol) of Me_2Zn (2.0 M solution in toluene), 120 μL (1.49 mmol) of CH_2I_2, and 153 mg (0.501 mmol) of imine **104** (24 h reaction time) afforded 99 mg (49%) of **280** as a 75:25 mixture of diastereomers. *syn*-**280** (colorless solid): mp 166-167 °C (EtOAc/hexane); IR (KBr) 3121, 2962, 2920, 2872, 2846, 1435, 1183, 1123, 1110, 1061, 897, 749, 726, 694 cm^{-1}; ^1H NMR δ 7.84-7.77 (m, 2 H), 7.67-7.61 (m, 2 H), 7.51-7.37 (m, 4 H), 7.29-7.17 (m, 5 H), 7.02-6.99 (m, 2 H), 4.79 (s, 1 H), 4.72 (s, 1 H), 4.12 (q, 1 H, *J* = 9.6 Hz), 3.39 (t, 1 H, *J* = 8.8 Hz), 2.34 (ddd, 1 H, *J* = 11.3, 7.9, 3.5 Hz), 2.00 (dqd, 1 H, *J* = 14.7, 7.4, 3.6 Hz), 1.65 (dq, 1 H, *J* = 14.8, 7.4 Hz), 1.57-1.42 (m, 2 H), 0.84 (t, 3 H, *J* = 7.3 Hz), 0.80 (t, 3 H, *J* = 7.3 Hz); ^{13}C NMR δ 149.63, 142.89, 142.84, 133.98, 132.74, 132.61, 132.29, 131.80, 131.77, 131.74, 131.68, 131.58, 131.54, 130.95, 128.49, 128.32, 128.15, 127.98, 127.78, 127.10, 126.68, 111.66, 58.61, 56.82, 56.76, 26.35, 23.12, 12.10, 11.54; EIMS *m/z* 404 ($[M+H]^+$, 1), 306 (100), 201 (93), 77 (86); HRMS (EI) *m/z* calcd for $C_{26}H_{30}NOP$ 403.2065, found 403.2052. *anti*-**280** (colorless solid): mp 164-165 °C (EtOAc/hexane); IR (KBr) 3197, 2961, 2932, 2873, 1436, 1185, 1124, 1109, 747, 725, 695 cm^{-1}; ^1H NMR δ 7.77-7.69 (m, 2 H), 7.60-7.53 (m, 2 H), 7.51-7.27 (m, 4 H), 7.20-7.04 (m, 7 H), 5.04 (s, 1 H), 4.96 (s, 1 H), 4.14 (td, 1 H, *J* = 9.2, 6.2 Hz), 3.60-3.50 (m, 1 H), 2.29 (ddd, 1 H, *J* = 10.7, 8.8, 4.2 Hz), 2.05 (dq, 1 H, *J* = 14.7, 7.4 Hz), 1.84 (dq, 1 H, *J* = 14.6, 7.3 Hz), 1.32 (ddq, 1 H, *J* = 14.0, 10.8, 7.3 Hz), 1.16 (dqd, 1 H, *J* = 14.2, 7.4, 4.4 Hz), 1.07 (t, 3 H, *J* = 7.3 Hz), 0.69 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR δ 150.73, 143.11, 134.08, 132.58, 132.45, 131.68, 131.65, 131.50, 131.37, 131.23, 130.79, 128.46, 128.29, 127.93, 127.89, 127.72, 127.46, 126.84, 112.49, 57.69, 57.60, 56.88, 24.31, 22.98, 12.09, 11.64; EIMS *m/z* 403 (M^+, 1), 306 (100), 201 (62), 91 (12), 77 (19); HRMS (EI) *m/z* calcd for $C_{26}H_{30}NOP$ 403.2065, found 403.2076.



syn-**281**

***N*-{(1*S**,2*R**)-2-[2-(*tert*-Butyldiphenylsilyl)oxyethyl]-1-phenylbut-3-enyl}-*P*,*P*-diphenylphosphinamide (*syn*-281).** According to the General Protocol D, 387 mg (1.50 mmol) of Cp_2ZrHCl, 510 mg (1.65 mmol) of alkyne **148**, 1.25 mL (2.50 mmol) of Me_2Zn (2.0 M solution in toluene), 120 μL (1.49 mmol) of CH_2I_2, and 153 mg (0.501 mmol) of imine **104** (12 h reaction time) afforded 227 mg (72%) of **281** as an 85:15 mixture of diastereomers. *syn*-**281** (colorless oil): IR (neat) 3196, 3070, 2930, 2857, 1438, 1428, 1191, 1110, 726, 700 cm^{-1}; ^1H

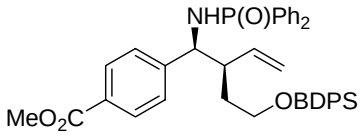
NMR δ 7.96-7.88 (m, 2 H), 7.80-7.72 (m, 2 H), 7.72-7.67 (m, 4 H), 7.57-7.30 (m, 14 H), 7.12-7.09 (m, 2 H), 5.47 (dt, 1 H, *J* = 17.2, 9.7 Hz), 5.22 (dd, 1 H, *J* = 17.3, 2.2 Hz), 5.20 (dd, 1 H, *J* = 9.8, 2.2 Hz), 4.26 (td, 1 H, *J* = 10.8, 5.1 Hz), 3.75 (dd, 1 H, *J* = 10.7, 6.9 Hz), 3.70-3.63 (m, 2 H), 2.89-2.80 (m, 1 H), 1.92 (dtd, 1 H, *J* = 13.4, 7.9, 3.3 Hz), 1.34-1.15 (m, 1 H), 1.10 (s, 9 H); ^{13}C NMR δ 141.02, 140.96, 137.22, 135.49, 135.46, 133.94, 133.76, 133.71, 132.78, 132.54, 132.41, 132.24, 131.75, 131.62, 131.57, 131.05, 129.45, 128.50, 128.34, 128.19, 128.02, 127.80, 127.52, 126.89, 119.12, 61.73, 57.91, 48.28, 48.22, 34.54, 26.80, 19.08; EIMS *m/z* 628 ([M-H]$^+$, 1), 572 (48), 306 (100), 201 (75); HRMS (EI) *m/z* calcd for $C_{36}H_{35}NO_2PSi$ [M-C_4H_9] 572.2175, found 572.2174.



syn-**282** *anti*-**282**

(4*R)-*O*-Triisopropylsilyl-4-{(*S**)-[(diphenylphosphinyl)amino](phenyl)methyl}hex-5-enoate (*syn*-282)** and **(4*S**)-*O*-triisopropylsilyl-4-{(*S**)-[(diphenylphosphinyl)amino]-(phenyl)methyl}hex-5-enoate (*anti*-282).** A solution of 324 mg (3.30 mmol) of 4-pentynoic acid in 6 mL of CH_2Cl_2 was treated with 710 μL (3.32 mmol) of TIPS-Cl and 225 mg (3.30 mmol) of imidazole, stirred at room temperature for 1 h, washed with H_2O and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in 1 mL of CH_2Cl_2, transferred into a suspension of 780 mg (3.02 mmol) of Cp_2ZrHCl in 2 mL of CH_2Cl_2, strirred for 5 min and concentrated *in vacuo*. A solution of the residue in 3 mL of toluene was cooled to -78 °C, treated with 1.50 mL (3.00 mmol) of Me_2Zn (2.0 M solution in toluene), warmed to room temperature over a period of 5 min, treated with 400 μL (4.97 mmol) of CH_2I_2, stirred for 2 min, cannulated into a suspension of 305 mg (1.00 mmol) of imine **104** in 1 mL of toluene, stirred at room temperature for 6 h, quenched with saturated NH_4Cl, diluted with EtOAc and saturated $NaHCO_3$, filtered through Celite, washed with H_2O and brine, dried ($MgSO_4$), filtered through a pad of Florisil and concentrated *in vacuo*. The residue was chromatographed on deactivated SiO_2 (1:4, hexanes/EtOAc containing 1% Et_3N) to yield 278 mg (48%) of **282** as a 62:38 mixture of diastereomers. *syn*-**282** (colorless oil): IR (neat) 3187, 2945, 2867, 1716, 1456, 1438, 1189, 1124, 1110, 1070, 918, 884, 751, 726, 700 cm^{-1}; ^{1}H NMR δ 7.85-7.78 (m, 2 H), 7.69-7.62 (m, 2 H), 7.50-7.39 (m, 4 H), 7.36-7.22 (m, 5 H), 7.03-7.00 (m, 2 H), 5.39 (dt, 1 H, *J* = 17.3, 9.6 Hz),

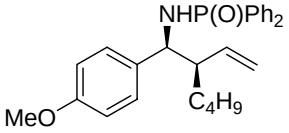
5.24-5.17 (m, 2 H), 4.18 (td, 1 H, *J* = 11.0, 5.1 Hz), 3.76 (dd, 1 H, *J* = 10.8, 6.4 Hz), 2.63-2.52 (m, 1 H), 2.30-2.24 (m, 2 H), 1.93-1.87 (m, 1 H), 1.29-1.14 (m, 4 H), 1.02 (d, 18 H, *J* = 7.3 Hz); ^{13}C NMR δ 173.37, 140.50, 136.67, 133.92, 132.64, 132.51, 132.23, 131.72, 131.59, 131.46, 130.70, 128.49, 128.32, 128.17, 128.00, 127.85, 127.42, 126.99, 120.03, 57.97, 51.63, 33.56, 27.25, 17.67, 11.75; EIMS *m/z* 575 (M^+, 1), 532 (46), 306 (100), 201 (91); HRMS (EI) *m/z* calcd for $C_{34}H_{46}NO_3PSi$ 575.2985, found 575.2999. *anti*-**282** (colorless oil): IR (neat) 2924, 2863, 1712, 1439, 1416, 1185, 1161, 1124, 1109, 1069, 997, 920, 883, 753, 724, 698 cm^{-1}; ^{1}H NMR δ 7.92-7.85 (m, 2 H), 7.75-7.68 (m, 2 H), 7.57-7.42 (m, 4 H), 7.35-7.24 (m, 5 H), 7.18-7.15 (m, 2 H), 5.73 (ddd, 1 H, *J* = 17.1, 10.2, 9.0 Hz), 5.34 (dd, 1 H, *J* = 10.3, 1.7 Hz), 5.19 (dd, 1 H, *J* = 17.2, 1.1 Hz), 4.21 (dt, 1 H, *J* = 10.1, 7.9 Hz), 3.53 (dd, 1 H, *J* = 8.4, 6.0 Hz), 2.52-2.22 (m, 3 H), 1.79-1.75 (m, 1 H), 1.65-1.59 (m, 1 H), 1.37-1.25 (m, 3 H), 1.09 (d, 18 H, *J* = 7.3 Hz); ^{13}C NMR δ 173.33, 142.08, 142.04, 138.24, 133.93, 132.68, 132.55, 132.42, 132.24, 131.75, 131.62, 131.47, 130.95, 128.50, 128.33, 128.10, 127.91, 127.23, 127.03, 118.97, 58.30, 51.25, 51.17, 33.44, 25.98, 17.72, 11.81; EIMS *m/z* 575 (M^+, 1), 532 (12), 306 (100), 201 (78); HRMS (EI) *m/z* calcd for $C_{34}H_{46}NO_3PSi$ 575.2985, found 575.2995.



syn-**283**

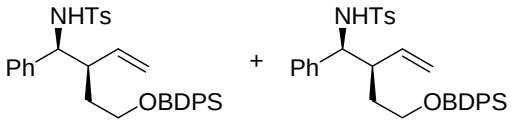
Methyl 4-[(1*S,2*R**)-2-[2-(*tert*-butyldiphenylsilyl)oxyethyl]-1-(diphenylphosphinyl-amino)-but-3-enyl]benzoate (*syn*-283).** According to the General Protocol D, 195 mg (0.756 mmol) of Cp_2ZrHCl, 255 mg (0.827 mmol) of alkyne **148**, 500 μL (1.00 mmol) of Me_2Zn (2.0 M solution in toluene), 100 μL (1.24 mmol) of CH_2I_2, and 91.0 mg (0.250 mmol) of imine **156** (12 h reaction time) afforded 118 mg (69%) of **283** as an 85:15 mixture of diastereomers. *syn*-**283** (colorless oil): IR (neat) 3191, 3071, 2952, 2931, 2857, 1721, 1437, 1282, 1190, 1110, 911, 728, 702 cm^{-1}; ^{1}H NMR δ 8.00 (d, 2 H, *J* = 8.3 Hz), 7.94-7.87 (m, 2 H), 7.77-7.65 (m, 6 H), 7.62-7.31 (m, 12 H), 7.17 (d, 2 H, *J* = 8.3 Hz), 5.40 (dt, 1 H, *J* = 17.9, 9.3 Hz), 5.21-5.15 (m, 2 H), 4.31 (td, 1 H, *J* = 10.6, 5.4 Hz), 4.01 (s, 3 H), 3.76 (dd, 1 H, *J* = 10.6, 6.9 Hz), 3.71-3.61 (m, 2 H), 2.89-2.79 (m, 1 H), 1.92 (dtd, 1 H, *J* = 13.3, 8.0, 3.2 Hz), 1.30-1.18 (m, 1 H), 1.09 (s, 9 H); ^{13}C NMR δ 167.06, 146.68, 146.62, 136.96, 135.66, 135.63, 133.84, 133.78, 133.75, 132.76, 132.61, 132.48, 132.05, 131.91, 131.79, 131.03, 129.69, 129.33, 128.96, 128.76, 128.60, 128.44, 128.27,

127.73, 119.70, 61.74, 57.87, 52.23, 48.34, 48.28, 34.62, 26.97, 19.24; EIMS *m/z* 688 ($[M+H]^+$, 1), 630 (80), 398 (19), 364 (100), 201 (99), 183 (33), 135 (46), 77 (70); HRMS (EI) *m/z* calcd for $C_{42}H_{45}NO_4PSi$ [M-H] 686.2856, found 686.2840.



syn-**284**

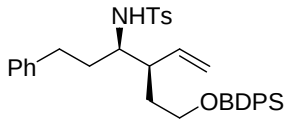
***N*-[(1*S**,2*R**)-2-Butyl-1-(4-methoxyphenyl)but-3-enyl]-*P*,*P*-diphenylphosphinamide (*syn*-284).** According to the General Protocol D, 390 mg (1.51 mmol) of Cp_2ZrHCl, 190 μL (1.65 mmol) of 1-hexyne, 1.00 mL (2.00 mmol) of Me_2Zn (2.0 M solution in toluene), 200 μL (2.48 mmol) of CH_2I_2, and 168 mg (0.501 mmol) of imine **158** (12 h reaction time) afforded 169 mg (79%) of **284** as an 83:17 mixture of diastereomers. *syn*-**284** (colorless solid): mp 155-156 °C (Et_2O/hexane); IR (KBr) 3218, 2956, 2916, 2857, 1516, 1436, 1252, 1183, 1123, 1108, 1072, 909, 825, 748, 724, 694 cm^{-1}; ^1H NMR δ 7.94-7.86 (m, 2 H), 7.79-7.72 (m, 2 H), 7.56-7.44 (m, 4 H), 7.38-7.31 (m, 2 H), 7.03 (d, 2 H, *J* = 8.7 Hz), 6.87 (d, 2 H, *J* = 8.7 Hz), 5.48 (dt, 1 H, *J* = 17.3, 9.7 Hz), 5.29 (dd, 1 H, *J* = 17.2, 2.5 Hz), 5.25 (dd, 1 H, *J* = 9.7, 2.5 Hz), 4.23 (td, 1 H, *J* = 11.1, 4.5 Hz), 3.88 (s, 3 H), 3.74 (dd, 1 H, *J* = 10.8, 6.4 Hz), 2.61 (tt, 1 H, *J* = 9.9, 4.2 Hz), 1.51-1.40 (m, 1 H), 1.32-1.18 (m, 4 H), 1.07-0.96 (m, 1 H), 0.88 (t, 3 H, *J* = 6.7 Hz); ^{13}C NMR δ 158.38, 137.92, 134.19, 133.09, 133.02, 132.77, 132.65, 132.52, 131.68, 131.65, 131.52, 131.49, 131.02, 128.59, 128.47, 128.31, 128.15, 127.98, 118.94, 113.05, 57.17, 55.14, 52.19, 52.15, 31.69, 29.53, 22.53, 13.96; FABMS *m/z* 456 ($[M+Na]^+$, 5), 434 ($[M+H]^+$, 28), 336 (20), 202 (17), 122 (100); HRMS (CI) *m/z* calcd for $C_{27}H_{33}NO_2P$ [M+H] 434.2249, found 434.2227.



syn-**285** *anti*-**285**

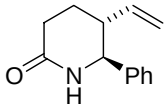
***N*-{(1*S**,2*R**)-2-[2-(*tert*-Butyldiphenylsilyl)oxyethyl]-1-phenylbut-3-enyl}-*S*-(4-methylphenyl)sulfonamide (*syn*-285)** and ***N*-{(1*S**,2*S**)-2-[2-(*tert*-butyldiphenylsilyl)oxy-ethyl]-1-phenylbut-3-enyl}-*S*-(4-methylphenyl)sulfonamide (*anti*-285).** According to the General Protocol D, 390 mg (1.51 mmol) of Cp_2ZrHCl, 510 mg (1.65 mmol) of alkyne **148**, 750 μL (1.50 mmol) of Me_2Zn (2.0 M solution in toluene), 200 μL (2.48 mmol) of CH_2I_2, and 130 mg (0.501 mmol) of imine **90** (2 h reaction time) afforded 238 mg (81%) of **285** as an

(inseparable) 60:40 mixture of diastereomers: IR (neat) 3280, 3070, 2930, 2857, 1428, 1326, 1162, 1111, 1093, 736, 702, 667 cm^{-1}; ^1H NMR δ 7.72-7.35 (m, 12 H), 7.25-7.11 (m, 6 H), 7.01-6.98 (m, 1 H), 5.56-5.07 (m, 4 H), 4.46 (dd, 0.6 H, *J* = 8.6, 5.5 Hz), 4.22 (dd, 0.4 H, *J* = 8.3, 5.3 Hz), 3.70-3.55 (m, 2 H), 2.75-2.64 (m, 1 H), 2.41 (s, 1.2 H), 2.39 (s, 1.8 H), 1.90-1.80 (m, 0.6 H), 1.57-1.47 (m, 0.4 H), 1.44-1.19 (m, 1 H), 1.11 (s, 5.4 H), 1.07 (s, 3.6 H); ^{13}C NMR δ 142.74, 139.30, 138.03, 137.71, 137.61, 137.40, 136.52, 135.49, 135.42, 133.62, 129.57, 129.50, 129.14, 129.02, 128.07, 127.80, 127.61, 127.58, 127.54, 127.23, 127.08, 127.04, 126.88, 119.67, 119.18, 61.19, 60.78, 60.71, 60.57, 46.77, 46.33, 33.90, 33.25, 26.81, 26.75, 21.38, 19.10; EIMS *m/z* 526 ($[M-C_4H_9]^+$, 42), 352 (83), 260 (96), 199 (68), 155 (68), 135 (46), 91 (100); HRMS (EI) *m/z* calcd for $C_{31}H_{32}NO_3SSi$ [M-C_4H_9] 526.1872, found 526.1869.



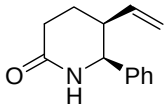
syn-**286**

***N*-{(1*S**,2*R**)-2-[2-(*tert*-Butyldiphenylsilyl)oxyethyl]-1-phenethylbut-3-enyl}-*S*-(4-methylphenyl)sulfonamide (*syn*-286).** According to the General Protocol D, 195 mg (0.756 mmol) of Cp_2ZrHCl, 255 mg (0.827 mmol) of alkyne **148**, 500 μL (1.00 mmol) of Me_2Zn (2.0 M solution in toluene), 100 μL (1.24 mmol) of CH_2I_2, and 72.0 mg (0.251 mmol) of imine **166** (4 h reaction time) afforded 134 mg (87%) of *syn*-**286** as a colorless oil: IR (thin film) 3280, 2930, 2857, 1428, 1327, 1160, 1111, 1094, 912, 816, 737, 702, 665 cm^{-1}; ^1H NMR δ 7.84 (d, 2 H, *J* = 8.3 Hz), 7.80-7.70 (m, 5 H), 7.54-7.45 (m, 6 H), 7.39-7.25 (m, 4 H), 7.20-7.15 (m, 2 H), 5.50 (dt, 1 H, *J* = 17.0, 9.9 Hz), 5.15 (dd, 1 H, *J* = 10.1, 1.9 Hz), 4.95 (dd, 1 H, *J* = 17.0, 1.8 Hz), 4.72 (d, 1 H, *J* = 9.7 Hz), 3.67-3.38 (m, 3 H), 2.84-2.71 (m, 1 H), 2.60-2.49 (m, 1 H), 2.44 (s, 3 H), 2.28-2.20 (m, 1 H), 1.92-1.81 (m, 1 H), 1.73-1.64 (m, 1 H), 1.61-1.32 (m, 2 H), 1.13 (s, 9 H); ^{13}C NMR δ 143.17, 141.63, 138.51, 136.86, 135.48, 135.46, 133.64, 129.60, 128.35, 128.31, 127.60, 126.93, 125.84, 119.03, 61.65, 56.96, 44.89, 33.95, 32.88, 32.01, 26.80, 21.45, 19.08; EIMS *m/z* 554 ($[M-C_4H_9]^+$, 66), 352 (46), 288 (70), 199 (67), 155 (31), 135 (37), 117 (69), 91 (100); HRMS (EI) *m/z* calcd for $C_{27}H_{32}NO_2P$ [M-C_4H_9] 554.2185, found 554.2188.



anti-**287**

(5*R,6*S**)-6-Phenyl-5-vinylpiperidin-2-one (*anti*-287).** A solution of 92.0 mg (0.160 mmol) of *syn*-**282** in 5 mL of a 1 N solution of HCl(g) in MeOH was stirred at room temperature for 12 h and concentrated *in vacuo*. The residue was dissolved in 3 mL of CH_2Cl_2, treated with 220 μL (1.58 mmol) of Et_3N and 75.0 μL (0.494 mmol) of diethyl cyanophosphonate, stirred for 16 h, filtered through a pad of Florisil and concentrated *in vacuo*. The residue was purified by preparative TLC (EtOAc) to yield 18 mg (56%) of *anti*-**287** as a colorless solid: mp 131-132 °C (Et_2O/hexane); IR (KBr) 3171, 3070, 2883, 1647, 1400, 1004, 917, 760, 702 cm^{-1}; ^1H NMR δ 7.38-7.22 (m, 5 H), 5.72 (bs, 1 H), 5.62 (ddd, 1 H, *J* = 17.3, 10.4, 7.1 Hz), 4.99 (d, 1 H, *J* = 10.4 Hz), 4.91 (d, 1 H, *J* = 17.2 Hz), 4.22 (d, 1 H, *J* = 9.3 Hz), 2.57-2.38 (m, 3 H), 2.03-1.95 (m, 1 H), 1.90-1.79 (m, 1 H); ^{13}C NMR δ 171.61, 140.73, 137.32, 128.61, 128.22, 127.21, 116.86, 62.69, 45.40, 30.55, 26.14; EIMS *m/z* 201 (M^+, 26), 173 (9), 147 (12), 118 (13), 106 (100); HRMS (EI) *m/z* calcd for $C_{13}H_{15}NO$ 201.1154, found 201.1158.

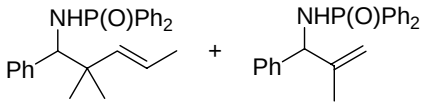


syn-**287**

(5*S,6*S**)-6-Phenyl-5-vinylpiperidin-2-one (*syn*-287).** A solution of 25.0 mg (0.0434 mmol) of *anti*-**282** in 5 mL of a 1 N solution of HCl(g) in MeOH was stirred at room temperature for 12 h and concentrated *in vacuo*. The residue was dissolved in 3 mL of CH_2Cl_2, treated with 60.0 μL (0.430 mmol) of Et_3N and 20.0 μL (0.132 mmol) of diethyl cyanophosphonate, stirred for 16 h, filtered through a pad of Florisil and concentrated *in vacuo*. The residue was purified by preparative TLC (EtOAc) to yield 6.0 mg (69%) of *syn*-**287** as a colorless solid: mp 108-109 °C (Et_2O/hexane); IR (thin film) 3200, 3061, 2933, 1660, 1404, 1353, 998, 915, 763, 700 cm^{-1}; ^1H NMR δ 7.37-7.26 (m, 3 H), 7.19-7.16 (m, 2 H), 5.89 (bs, 1 H), 5.46 (ddd, 1 H, *J* = 17.3, 10.1, 8.3 Hz), 5.01 (d, 1 H, *J* = 16.9 Hz), 4.99 (d, 1 H, *J* = 11.1 Hz), 4.68 (dd, 1 H, *J* = 4.9, 2.5 Hz), 2.82 (tt, 1 H, *J* = 8.7, 4.4 Hz), 2.67-2.44 (m, 2 H), 1.94-1.77 (m, 2 H); ^{13}C NMR δ 172.03, 138.90, 136.63, 128.23, 127.87, 127.52, 117.12, 60.38, 42.65, 29.66, 23.33; EIMS *m/z* 201 (M^+, 6), 173 (2), 147 (3), 119 (4), 106 (37), 84 (100); HRMS (EI) *m/z* calcd for $C_{13}H_{15}NO$ 201.1154, found 201.1156.

Attempted preparation of 2-butyl-1-phenylbut-3-en-1-ol using the General Protocol D. A suspension of 97.0 mg (0.376 mmol) of Cp_2ZrHCl in 2 mL of CH_2Cl_2 was treated at room temperature with 45.0 μL (0.392 mmol) of 1-hexyne. After 5 min, the yellow solution was cooled to -78 °C, treated with 190 μL (0.380 mmol) of Me_2Zn (2.0 M solution in toluene), warmed to 0 °C over a period of 5 min, treated with 90.0 μL (1.12 mmol) of CH_2I_2, stirred for 2 min, treated with 25.0 μL (0.246 mmol) of PhCHO, stirred at 0 °C for 30 min, quenched with saturated NH_4Cl, diluted with EtOAc, filtered through Celite, washed with H_2O and brine, dried ($MgSO_4$), filtered through a pad of Florisil and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (4:1, hexanes/EtOAc) to yield 41 mg (88%) of **33**.

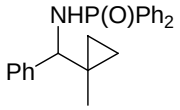
Attempted preparation of 280 using a B-Zn transmetalation. A solution of 190 μL (1.67 mmol) of 3-hexyne in 2 mL of CH_2Cl_2 was cooled to 0 °C, treated with 500 μL (0.500 mmol) of borane (1.0 M solution in THF), and stirred at 0 °C for 1 h. The mixture was treated with 750 μL (1.50 mmol) of Me_2Zn (2.0 M solution in toluene), stirred for 2 min, treated with 200 μL (2.48 mmol) of CH_2I_2, warmed to room temperature, treated with a solution of 153 mg (0.501 mmol) of imine **104** in 2 mL of CH_2Cl_2, stirred at room temperature for 16 h, quenched with saturated NH_4Cl, diluted with EtOAc, filtered through Celite, washed with H_2O, saturated $NaHCO_3$ and brine, dried ($MgSO_4$), filtered through a pad of Florisil and concentrated *in vacuo*. The residue was chromatographed on deactivated SiO_2 (1:9, hexanes/EtOAc contain-ing 1% Et_3N) to yield 97 mg (50%) of **147**.



293 **294**

(*E*)-*N*-(2,2-Dimethyl-1-phenylpent-3-enyl)-*P,P*-diphenylphosphinamide (293) and *N*-(2-methyl-1-phenylallyl)-*P,P*-diphenylphosphinamide (294). A solution of 876 mg (3.00 mmol) of Cp_2ZrCl_2 in 10 mL of THF was cooled to -78 °C, treated with 3.80 mL (6.08 mmol) of *n*-BuLi (1.6 M solution in hexanes), stirred at -78 °C for 1 h, treated with 300 μL (3.38 mmol) of 2-bromopropene, warmed to room temperature over 5 min, stirred for 1 h and concentrated *in vacuo*. The residue was suspended in 2 mL of toluene, cooled to -78 °C, treated with 1.50 mL (3.00 mmol) of Me_2Zn (2.0 M solution in toluene), warmed to room temperature over 5 min, stirred for 2 h, treated with a solution of 153 mg (0.501 mmol) of imine **104** in 0.5 mL of THF

and 2 mL of toluene, stirred at room temperature for 12 h, quenched with saturated NH_4Cl, diluted with EtOAc and saturated $NaHCO_3$, filtered through Celite, washed with H_2O and brine, dried ($MgSO_4$), filtered through a pad of Florisil and concentrated *in vacuo*. The residue was chromatographed on deactivated SiO_2 (1:4, hexanes/EtOAc containing 1% Et_3N) to yield 88 mg (45%) of **293** and 27 mg (16%) of **294** as colorless solids. **293**: R_f 0.61 (1:4, hexanes/EtOAc); mp 134-135 °C (Et_2O/hexane); IR (KBr) 3323, 3059, 3017, 2967, 2937, 2875, 1434, 1182, 1125, 1068, 754, 724, 707, 692 cm^{-1}; ^1H NMR δ 7.80-7.73 (m, 2 H), 7.59-7.52 (m, 2 H), 7.49-7.27 (m, 5 H), 7.21-7.15 (m, 4 H), 6.99-6.96 (m, 2 H), 5.53-5.36 (m, 2 H), 3.83 (t, 1 H, *J* = 10.6 Hz), 3.45 (t, 1 H, *J* = 8.7 Hz), 1.70 (d, 3 H, *J* = 5.1 Hz), 1.22 (s, 3 H), 0.81 (s, 3 H); ^{13}C NMR δ 141.68, 141.64, 136.15, 134.37, 132.84, 132.80, 132.67, 131.91, 131.78, 131.53, 131.50, 131.10, 128.61, 128.45, 128.10, 127.94, 127.49, 126.84, 125.48, 63.77, 40.87, 40.81, 26.06, 25.92, 18.45; EIMS *m/z* 390 ($[M+H]^+$, 1), 306 (100), 201 (93); HRMS (EI) *m/z* calcd for $C_{25}H_{29}NOP$ [M+H] 390.1987, found 390.1971. **294**: R_f 0.53 (1:4, hexanes/EtOAc); mp 135-136 °C (Et_2O/hexane); IR (KBr) 3192, 1438, 1184, 1123, 1109, 725, 701 cm^{-1}; ^1H NMR δ 8.04-7.89 (m, 4 H), 7.61-7.31 (m, 11 H), 5.22 (s, 1 H), 5.13 (s, 1 H), 4.77 (t, 1 H, *J* = 10.6 Hz), 3.43 (dd, 1 H, *J* = 10.6, 6.6 Hz), 1.70 (s, 3 H); ^{13}C NMR δ 145.72, 145.66, 141.69, 141.63, 133.50, 133.11, 132.39, 132.27, 132.20, 132.07, 131.89, 131.85, 131.82, 131.79, 131.40, 128.55, 128.51, 128.45, 128.34, 128.29, 127.31, 127.01, 126.68, 112.54, 60.21, 19.79; EIMS *m/z* 347 (M^+, 19), 306 (26), 201 (72), 193 (43), 146 (95), 99 (100), 77 (59); HRMS (EI) *m/z* calcd for $C_{22}H_{22}NOP$ 347.1439, found 347.1431.

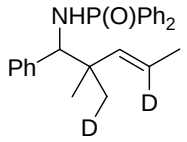


295

***N*-[(1-Methylcyclopropyl)phenylmethyl]-*P*,*P*-diphenylphosphinamide (295).**

A solution of 438 mg (1.50 mmol) of Cp_2ZrCl_2 in 5 mL of THF was cooled to -78 °C, treated with 1.88 mL (3.01 mmol) of *n*-BuLi (1.6 M solution in hexanes), stirred at -78 °C for 1 h, treated with 140 μL (1.57 mmol) of 2-bromopropene, warmed to room temperature over 5 min, stirred for 1 h and concentrated *in vacuo*. The residue was dissolved in 3 mL of CH_2Cl_2, cooled to -78 °C, treated with 750 μL (3.00 mmol) of Me_2Zn (2.0 M solution in toluene), warmed to room temperature over 5 min and treated with a solution of 153 mg (0.501 mmol) of imine **104** in 1 mL of CH_2Cl_2. The mixture was heated at reflux for 1 h, treated with 200 μL (2.48 mmol)

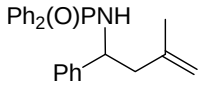
of CH_2I_2, heated at reflux for 12 h, quenched with saturated NH_4Cl, diluted with EtOAc and saturated $NaHCO_3$, filtered through Celite, washed with H_2O and brine, dried ($MgSO_4$), filtered through a pad of Florisil and concentrated *in vacuo*. The residue was chromatographed on deactivated SiO_2 (1:4, hexanes/EtOAc containing 1% Et_3N) to yield 81 mg (42%) of **293** and 25 mg (14%) of **295** as a colorless oil. **295**: IR (thin film) 3199, 3056, 2957, 2869, 1452, 1439, 1186, 1123, 1108, 1063, 751, 723, 698 cm^{-1}; ^1H NMR δ 7.93-7.86 (m, 2 H), 7.74-7.68 (m, 2 H), 7.52-7.36 (m, 4 H), 7.31-7.19 (m, 7 H), 3.77 (t, 1 H, J = 10.5 Hz), 3.42 (dd, 1 H, J = 9.5, 6.0 Hz), 1.01 (s, 3 H), 0.68-0.64 (m, 1 H), 0.60-0.54 (m, 1 H), 0.40-0.30 (m, 2 H); ^{13}C NMR δ 142.44, 142.37, 132.67, 132.55, 132.19, 132.07, 131.93, 131.81, 128.65, 128.49, 128.42, 128.25, 128.18, 127.16, 127.02, 61.57, 21.57, 21.51, 19.89, 12.94, 12.40; EIMS *m/z* 361 (M^+, 7), 306 (100), 201 (91), 160 (53), 91 (25), 77 (26); HRMS (EI) *m/z* calcd for $C_{23}H_{24}NOP$ 361.1596, found 361.1592.



296

(*E*)-*N*-(4-Deutero-2-(deuteromethyl)-2-methyl-1-phenylpent-3-enyl)-*P*,*P*-diphenyl-phosphinamide (296). A solution of 590 mg (2.02 mmol) of Cp_2ZrCl_2 in 6 mL of THF was cooled to -78 °C, treated with 2.50 mL (4.00 mmol) of *n*-BuLi (1.6 M solution in hexanes), stirred at -78 °C for 1 h, treated with 270 μL (3.04 mmol) of 2-bromopropene, warmed to room temperature over 5 min, stirred for 1 h and concentrated *in vacuo*. The residue was suspended in 3 mL of toluene, cooled to -78 °C, treated with 1.00 mL (2.00 mmol) of Me_2Zn (2.0 M solution in toluene), warmed to room temperature over 5 min, and cannulated into a suspension of 153 mg (0.501 mmol) of imine **104** in 1 mL of toluene. The mixture was stirred at room temperature for 12 h, quenched with saturated NH_4Cl, diluted with EtOAc and saturated $NaHCO_3$, filtered through Celite, washed with H_2O and brine, dried ($MgSO_4$), filtered through a pad of Florisil and concentrated *in vacuo*. The residue was chromatographed on deactivated SiO_2 (1:4, hexanes/ EtOAc containing 1% Et_3N) to yield 90 mg (46%) of **296** and 46 mg (6%) of **294** as a colorless solid. **296**: mp 133-134 °C (Et_2O/hexane); IR (thin film) 3207, 3055, 2958, 2929, 1454, 1436, 1183, 1125, 1107, 1068, 908, 749, 726, 696 cm^{-1}; ^1H NMR δ 7.82-7.75 (m, 2 H), 7.61-7.48 (m, 2 H), 7.47-7.32 (m, 4 H), 7.24-7.17 (m, 5 H), 7.01-6.98 (m, 2 H), 5.41 (bs, 1 H), 3.85 (t, 1 H, J =

10.6 Hz), 3.47 (dd, 1 H, *J* = 9.7, 7.7 Hz), 1.71 (d, 3 H, *J* = 0.8 Hz), 1.22 (s, 2 H), 0.83 (s, 3 H); ^{13}C NMR δ 141.57, 141.53, 135.87, 134.26, 132.68, 132.55, 131.78, 131.66, 131.40, 131.36, 130.96, 128.48, 128.32, 127.97, 127.80, 127.35, 126.69, 125.09 (t, 1 C, *J* = 22.7 Hz), 63.61, 40.66, 40.59, 25.93, 25.48 (t, 1 C, *J* = 19.5 Hz), 18.19; ^{2}H NMR (77 MHz) δ 5.51, 1.18; EIMS *m/z* 392 ([M+H]$^{+}$, 1), 306 (100), 201 (77), 77 (24); HRMS (EI) *m/z* calcd for $C_{25}H_{27}D_2NOP$ [M+H] 392.2112 found 392.2104.

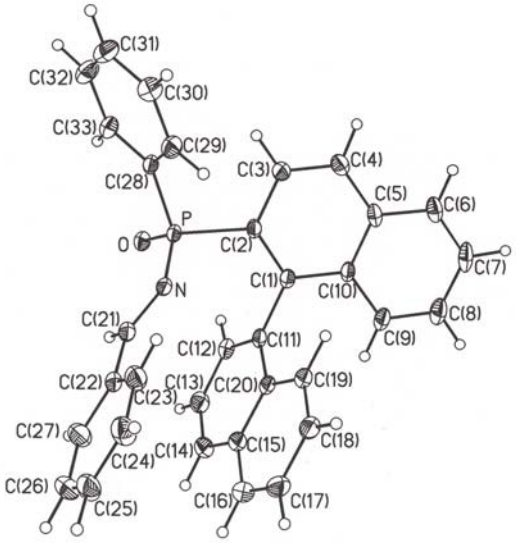


304

***N*-(3-Methyl-1-phenylbut-3-enyl)-*P*,*P*-diphenylphosphinamide (304).** A solution of 584 mg (2.00 mmol) of Cp_2ZrCl_2 in 6 mL of THF was cooled to -78 °C, treated with 2.50 mL (4.00 mmol) of *n*-BuLi (1.6 M solution in hexanes), stirred at -78 °C for 1 h, treated with 200 μL (2.25 mmol) of 2-bromopropene, warmed to room temperature over 5 min, stirred for 1 h and concentrated *in vacuo*. The residue was suspended in 2 mL of toluene, cooled to -78 °C, treated with 1.00 mL (2.00 mmol) of Me_2Zn (2.0 M solution in toluene), warmed to room temperature over 5 min, treated with 200 μL (2.48 mmol) of CH_2I_2, stirred for 2 min, treated with a solution of 153 mg (0.501 mmol) of imine **104** in 0.5 mL of CH_2Cl_2 and 1.5 mL of toluene, stirred at room temperature for 4 h, quenched with saturated NH_4Cl, diluted with EtOAc and saturated $NaHCO_3$, filtered through Celite, washed with H_2O and brine, dried ($MgSO_4$), filtered through a pad of Florisil and concentrated *in vacuo*. The residue was chromatographed on deactivated SiO_2 (1:9, hexanes/EtOAc containing 1% Et_3N) to yield 136 mg (75%) of **304** as a colorless solid: mp 165-166 °C (Et_2O/hexane); IR (thin film) 3182, 3058, 2910, 1437, 1186, 1123, 1109, 724, 696 cm^{-1}; ^{1}H NMR δ 7.87-7.79 (m, 2 H), 7.76-7.67 (m, 2 H), 7.51-7.33 (m, 4 H), 7.31-7.14 (m, 7 H), 4.77 (s, 1 H), 4.68 (s, 1 H), 4.36 (qn, 1 H, *J* = 6.3 Hz), 3.28 (dd, 1 H, *J* = 7.9, 6.0 Hz), 2.61 (dd, 1 H, *J* = 13.6, 7.3 Hz), 2.52 (dd, 1 H, *J* = 13.7, 7.0 Hz), 1.57 (s, 3 H); ^{13}C NMR δ 143.49, 142.00, 133.88, 132.86, 132.51, 132.38, 132.19, 131.83, 131.71, 131.62, 131.13, 128.52, 128.35, 128.30, 128.26, 128.09, 127.06, 126.56, 114.40, 53.39, 48.20, 48.13, 22.26; EIMS *m/z* 361 (M^{+}, 1), 306 (74), 201 (100); HRMS (EI) *m/z* calcd for $C_{23}H_{24}NOP$ 361.1596, found 361.1593.

Appendix A

X-ray Structure and Data of Binaphthyl-Phenyl Phosphinimine 219



Appendix A, Table 1. Crystal data and structure refinement.

Identification code	ck1203s	
Empirical formula	$C_{33}H_{24}NOP$	
Formula weight	481.50	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.5978(16) Å	α = 106.997(3)°
	b = 10.7312(16) Å	β = 97.186(3)°
	c = 13.330(2) Å	γ = 114.688(3)°
Volume	1262.9(3) $Å^3$	
Z	2	
Density (calculated)	1.266 Mg/m^3	
Absorption coefficient	0.136 mm^{-1}	
F(000)	504	
Crystal size	0.27 x 0.18 x 0.18 mm^3	
Theta range for data collection	1.67 to 32.48°	
Index ranges	$-15 \le h \le 15$, $-16 \le k \le 15$, $-19 \le l \le 19$	
Reflections collected	16001	
Independent reflections	8473 [R(int) = 0.0551]	
Completeness to theta = 32.48°	92.9%	
Absorption correction	None	
Max. and min. transmission	0.9760 and 0.9643	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8473 / 0 / 421	
Goodness-of-fit on F^2	1.011	
Final R indices [I>2sigma(I)]	R1 = 0.0736, wR2 = 0.1766	
R indices (all data)	R1 = 0.1153, wR2 = 0.1996	
Largest diff. peak and hole	0.862 and -0.484 $e.Å^{-3}$	

Appendix A, Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for ck1203s. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
P	2297(1)	5153(1)	1897(1)	16(1)
O	2456(2)	4133(2)	961(1)	19(1)
N	3572(2)	5987(2)	3101(1)	17(1)
C(1)	3382(2)	7871(2)	1630(2)	16(1)
C(2)	2169(2)	6667(2)	1637(2)	16(1)
C(3)	783(2)	6561(2)	1372(2)	20(1)
C(4)	605(2)	7651(2)	1148(2)	22(1)
C(5)	1819(2)	8914(2)	1166(2)	20(1)
C(6)	1669(3)	10071(2)	944(2)	24(1)
C(7)	2839(3)	11246(2)	902(2)	29(1)
C(8)	4200(3)	11303(3)	1068(2)	28(1)
C(9)	4390(3)	10220(2)	1299(2)	23(1)
C(10)	3210(2)	9002(2)	1372(2)	17(1)
C(11)	4844(2)	7967(2)	1848(2)	17(1)
C(12)	5155(2)	7086(2)	1053(2)	19(1)
C(13)	6518(2)	7126(2)	1219(2)	24(1)
C(14)	7555(2)	8046(2)	2201(2)	25(1)
C(15)	7289(2)	8982(2)	3048(2)	20(1)
C(16)	8358(2)	9933(3)	4067(2)	25(1)
C(17)	8088(3)	10818(3)	4882(2)	26(1)
C(18)	6746(2)	10813(2)	4713(2)	22(1)
C(19)	5687(2)	9904(2)	3732(2)	18(1)
C(20)	5925(2)	8960(2)	2872(2)	17(1)
C(21)	4631(2)	5705(2)	3202(2)	19(1)
C(22)	5739(2)	6366(2)	4250(2)	19(1)
C(23)	5576(3)	7172(3)	5201(2)	25(1)
C(24)	6645(3)	7828(3)	6187(2)	30(1)
C(25)	7883(3)	7678(3)	6217(2)	33(1)
C(26)	8060(3)	6872(3)	5278(2)	34(1)
C(27)	6977(3)	6202(3)	4290(2)	28(1)
C(28)	705(2)	4212(2)	2290(2)	17(1)
C(29)	396(2)	4913(2)	3212(2)	22(1)
C(30)	-829(2)	4123(3)	3485(2)	25(1)
C(31)	-1745(3)	2622(3)	2853(2)	28(1)
C(32)	-1440(3)	1921(3)	1944(2)	28(1)
C(33)	-214(2)	2708(2)	1663(2)	21(1)

Appendix A, Table 3. Bond lengths [Å] and angles [°] for ck1203s.

P-O	1.4800(15)	O-P-N	118.46(9)	C(14)-C(13)-C(12)	119.6(2)
P-N	1.6764(18)	O-P-C(28)	112.25(9)	C(13)-C(14)-C(15)	120.9(2)
P-C(28)	1.802(2)	N-P-C(28)	100.60(9)	C(16)-C(15)-C(14)	121.1(2)
P-C(2)	1.8114(19)	O-P-C(2)	113.64(9)	C(16)-C(15)-C(20)	119.49(19)
N-C(21)	1.280(3)	N-P-C(2)	104.07(9)	C(14)-C(15)-C(20)	119.46(19)
C(1)-C(2)	1.394(3)	C(28)-P-C(2)	106.38(9)	C(17)-C(16)-C(15)	120.7(2)
C(1)-C(10)	1.427(3)	C(21)-N-P	119.98(15)	C(16)-C(17)-C(18)	120.2(2)
C(1)-C(11)	1.494(3)	C(2)-C(1)-C(10)	119.27(18)	C(19)-C(18)-C(17)	120.5(2)
C(2)-C(3)	1.415(3)	C(2)-C(1)-C(11)	121.10(17)	C(18)-C(19)-C(20)	120.7(2)
C(3)-C(4)	1.367(3)	C(10)-C(1)-C(11)	119.60(17)	C(19)-C(20)-C(15)	118.37(18)
C(4)-C(5)	1.418(3)	C(1)-C(2)-C(3)	120.11(18)	C(19)-C(20)-C(11)	122.79(18)
C(5)-C(6)	1.423(3)	C(1)-C(2)-P	121.53(15)	C(15)-C(20)-C(11)	118.82(18)
C(5)-C(10)	1.423(3)	C(3)-C(2)-P	118.26(15)	N-C(21)-C(22)	121.77(19)
C(6)-C(7)	1.372(4)	C(4)-C(3)-C(2)	121.3(2)	C(23)-C(22)-C(27)	119.5(2)
C(7)-C(8)	1.405(4)	C(3)-C(4)-C(5)	120.1(2)	C(23)-C(22)-C(21)	120.65(19)
C(8)-C(9)	1.368(3)	C(4)-C(5)-C(6)	121.3(2)	C(27)-C(22)-C(21)	119.8(2)
C(9)-C(10)	1.421(3)	C(4)-C(5)-C(10)	119.39(18)	C(22)-C(23)-C(24)	120.5(2)
C(11)-C(12)	1.374(3)	C(6)-C(5)-C(10)	119.2(2)	C(25)-C(24)-C(23)	119.6(2)
C(11)-C(20)	1.432(3)	C(7)-C(6)-C(5)	120.8(2)	C(26)-C(25)-C(24)	120.7(2)
C(12)-C(13)	1.414(3)	C(6)-C(7)-C(8)	119.7(2)	C(25)-C(26)-C(27)	119.6(2)
C(13)-C(14)	1.369(3)	C(9)-C(8)-C(7)	121.1(2)	C(22)-C(27)-C(26)	120.1(2)
C(14)-C(15)	1.420(3)	C(8)-C(9)-C(10)	120.8(2)	C(29)-C(28)-C(33)	119.49(19)
C(15)-C(16)	1.416(3)	C(9)-C(10)-C(5)	118.27(18)	C(29)-C(28)-P	122.66(15)
C(15)-C(20)	1.425(3)	C(9)-C(10)-C(1)	122.05(19)	C(33)-C(28)-P	117.81(16)
C(16)-C(17)	1.366(3)	C(5)-C(10)-C(1)	119.68(18)	C(30)-C(29)-C(28)	119.98(19)
C(17)-C(18)	1.410(3)	C(12)-C(11)-C(20)	119.48(19)	C(29)-C(30)-C(31)	120.2(2)
C(18)-C(19)	1.376(3)	C(12)-C(11)-C(1)	119.42(18)	C(32)-C(31)-C(30)	120.0(2)
C(19)-C(20)	1.417(3)	C(20)-C(11)-C(1)	121.10(17)	C(31)-C(32)-C(33)	120.1(2)
C(21)-C(22)	1.465(3)	C(11)-C(12)-C(13)	121.8(2)	C(32)-C(33)-C(28)	120.2(2)
C(22)-C(23)	1.388(3)				
C(22)-C(27)	1.391(3)				
C(23)-C(24)	1.388(3)				
C(24)-C(25)	1.385(4)				
C(25)-C(26)	1.382(4)				
C(26)-C(27)	1.396(3)				
C(28)-C(29)	1.395(3)				
C(28)-C(33)	1.396(3)				
C(29)-C(30)	1.385(3)				
C(30)-C(31)	1.393(3)				
C(31)-C(32)	1.381(3)				
C(32)-C(33)	1.391(3)				

Appendix A, Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for ck1203s. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2(a^*)^2U^{11} + ... + 2hk(a^*)(b^*)U^{12}]$.

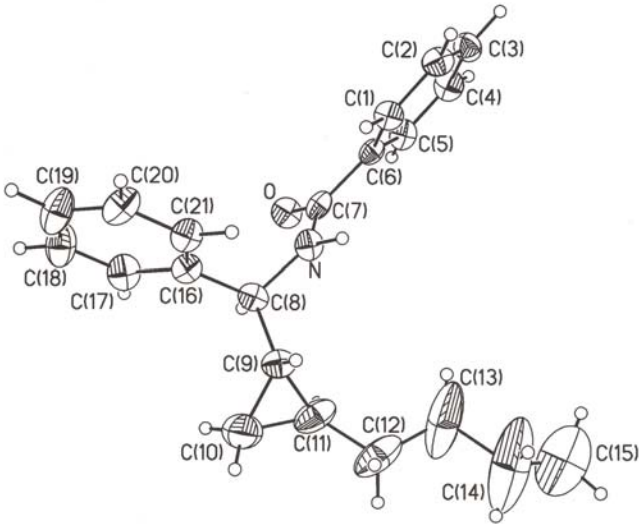
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P	17(1)	11(1)	18(1)	6(1)	3(1)	6(1)
O	21(1)	14(1)	22(1)	5(1)	5(1)	9(1)
N	16(1)	13(1)	20(1)	8(1)	2(1)	5(1)
C(1)	19(1)	13(1)	17(1)	6(1)	4(1)	8(1)
C(2)	19(1)	13(1)	17(1)	6(1)	3(1)	8(1)
C(3)	18(1)	18(1)	22(1)	8(1)	2(1)	8(1)
C(4)	23(1)	22(1)	21(1)	7(1)	3(1)	14(1)
C(5)	29(1)	17(1)	17(1)	6(1)	3(1)	15(1)
C(6)	35(1)	21(1)	19(1)	6(1)	0(1)	18(1)
C(7)	51(2)	18(1)	22(1)	8(1)	3(1)	21(1)
C(8)	40(1)	19(1)	28(1)	13(1)	6(1)	14(1)
C(9)	28(1)	15(1)	25(1)	10(1)	6(1)	9(1)
C(10)	22(1)	12(1)	18(1)	6(1)	3(1)	9(1)
C(11)	19(1)	12(1)	21(1)	8(1)	6(1)	9(1)
C(12)	23(1)	14(1)	21(1)	7(1)	7(1)	9(1)
C(13)	25(1)	23(1)	29(1)	11(1)	14(1)	14(1)
C(14)	22(1)	24(1)	34(1)	12(1)	10(1)	14(1)
C(15)	18(1)	18(1)	26(1)	11(1)	8(1)	9(1)
C(16)	20(1)	24(1)	30(1)	10(1)	4(1)	10(1)
C(17)	21(1)	22(1)	26(1)	7(1)	0(1)	6(1)
C(18)	23(1)	18(1)	24(1)	8(1)	6(1)	8(1)
C(19)	19(1)	15(1)	21(1)	8(1)	6(1)	8(1)
C(20)	18(1)	13(1)	22(1)	9(1)	7(1)	7(1)
C(21)	19(1)	15(1)	22(1)	8(1)	2(1)	8(1)
C(22)	19(1)	15(1)	24(1)	10(1)	2(1)	8(1)
C(23)	27(1)	24(1)	25(1)	9(1)	3(1)	13(1)
C(24)	36(1)	29(1)	23(1)	7(1)	0(1)	17(1)
C(25)	34(1)	29(1)	31(1)	9(1)	-8(1)	15(1)
C(26)	26(1)	31(1)	42(2)	12(1)	-2(1)	16(1)
C(27)	26(1)	29(1)	30(1)	9(1)	3(1)	16(1)
C(28)	18(1)	12(1)	19(1)	6(1)	2(1)	6(1)
C(29)	23(1)	17(1)	24(1)	5(1)	4(1)	8(1)
C(30)	25(1)	25(1)	24(1)	9(1)	7(1)	11(1)
C(31)	23(1)	26(1)	28(1)	14(1)	7(1)	4(1)
C(32)	25(1)	17(1)	29(1)	7(1)	4(1)	2(1)
C(33)	23(1)	15(1)	22(1)	6(1)	6(1)	7(1)

Appendix A, Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for ck1203s.

	x	y	z	U(eq)
H(3)	-70(30)	5680(30)	1340(20)	24(6)
H(4)	-390(30)	7500(30)	900(20)	32(7)
H(6)	700(30)	10010(30)	870(20)	26(7)
H(7)	2670(30)	12010(30)	780(20)	27(7)
H(8)	5030(30)	12130(30)	1030(20)	27(7)
H(9)	5320(30)	10270(30)	1380(20)	32(7)
H(12)	4460(30)	6400(30)	360(20)	22(6)
H(13)	6750(30)	6530(30)	640(20)	35(8)
H(14)	8490(30)	8090(30)	2350(20)	33(7)
H(16)	9310(30)	9960(30)	4190(20)	28(7)
H(17)	8830(30)	11490(30)	5560(20)	31(7)
H(18)	6580(30)	11450(30)	5310(20)	37(8)
H(19)	4710(30)	9890(30)	3610(20)	33(7)
H(21)	4790(30)	5110(30)	2570(20)	34(7)
H(23)	4720(30)	7220(30)	5190(20)	37(8)
H(24)	6490(30)	8260(30)	6840(20)	39(8)
H(25)	8680(30)	8110(30)	6910(30)	44(8)
H(26)	8980(30)	6820(30)	5280(30)	48(9)
H(27)	7080(30)	5670(30)	3590(20)	41(8)
H(29)	1030(30)	5980(30)	3670(20)	30(7)
H(30)	-1030(30)	4650(30)	4140(20)	22(6)
H(31)	-2590(30)	2090(30)	3070(20)	45(8)
H(32)	-2120(30)	850(30)	1510(20)	40(8)
H(33)	50(30)	2280(30)	1070(20)	21(6)

Appendix B

X-ray Structure and Data of Benzamide 268.



Appendix B, Table 1. Crystal data and structure refinement for ck102s.

Identification code	ck102s	
Empirical formula	$C_{21}H_{25}NO$	
Formula weight	307.42	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 5.3218(6) Å	α = 82.892(2)°
	b = 9.5102(10) Å	β = 82.762(2)°
	c = 17.900(2) Å	γ = 87.377(3)°
Volume	891.38(17) $Å^3$	
Z	2	
Density (calculated)	1.145 Mg/m^3	
Absorption coefficient	0.069 mm^{-1}	
F(000)	332	
Crystal size	0.27 x 0.03 x 0.03 mm^3	
Theta range for data collection	2.16 to 32.52°	
Index ranges	$-8 \le h \le 8$, $-13 \le k \le 13$, $-26 \le l \le 25$	
Reflections collected	11657	
Independent reflections	6038 [R(int) = 0.1076]	
Completeness to theta = 32.52°	93.6%	
Absorption correction	None	
Max. and min. transmission	0.9979 and 0.9815	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6038 / 0 / 212	
Goodness-of-fit on F^2	0.987	
Final R indices [I>2sigma(I)]	R1 = 0.1098, wR2 = 0.1907	
R indices (all data)	R1 = 0.2921, wR2 = 0.2549	
Largest diff. peak and hole	0.582 and -0.362 $e.Å^{-3}$	

Appendix B, Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for ck102s. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O	8439(4)	451(2)	3148(1)	35(1)
N	4293(5)	714(3)	2976(2)	30(1)
C(1)	3226(6)	-916(3)	4470(2)	29(1)
C(2)	2738(6)	-1919(4)	5099(2)	34(1)
C(3)	4500(6)	-2986(4)	5266(2)	35(1)
C(4)	6784(7)	-3048(4)	4791(2)	37(1)
C(5)	7294(6)	-2053(3)	4174(2)	32(1)
C(6)	5516(6)	-981(3)	4004(2)	25(1)
C(7)	6202(6)	116(3)	3341(2)	28(1)
C(8)	4648(6)	1887(3)	2367(2)	29(1)
C(9)	3028(6)	1691(4)	1754(2)	34(1)
C(10)	3768(9)	2398(5)	967(2)	66(1)
C(11)	3993(7)	824(5)	1138(2)	52(1)
C(12)	2266(8)	-152(5)	854(2)	69(2)
C(13)	2236(11)	-1598(5)	1265(5)	128(3)
C(14)	554(13)	-2589(7)	926(6)	177(4)
C(15)	1253(14)	-3911(8)	932(5)	154(3)
C(16)	4131(6)	3307(3)	2662(2)	28(1)
C(17)	5892(6)	4370(4)	2498(2)	39(1)
C(18)	5424(7)	5657(4)	2777(2)	49(1)
C(19)	3178(7)	5912(4)	3230(2)	51(1)
C(20)	1429(6)	4871(4)	3390(2)	40(1)
C(21)	1874(6)	3584(4)	3112(2)	34(1)

Appendix B, Table 3. Bond lengths [Å] and angles [°] for ck102s.

O-C(7)	1.242(3)	C(7)-N-C(8)	122.8(3)
N-C(7)	1.343(4)	C(2)-C(1)-C(6)	119.8(3)
N-C(8)	1.462(4)	C(3)-C(2)-C(1)	120.7(3)
C(1)-C(2)	1.389(4)	C(2)-C(3)-C(4)	119.0(3)
C(1)-C(6)	1.391(4)	C(5)-C(4)-C(3)	120.7(3)
C(2)-C(3)	1.381(4)	C(4)-C(5)-C(6)	120.3(3)
C(3)-C(4)	1.397(5)	C(5)-C(6)-C(1)	119.5(3)
C(4)-C(5)	1.370(4)	C(5)-C(6)-C(7)	118.3(3)
C(5)-C(6)	1.391(4)	C(1)-C(6)-C(7)	122.1(3)
C(6)-C(7)	1.499(4)	O-C(7)-N	122.3(3)
C(8)-C(16)	1.511(4)	O-C(7)-C(6)	120.8(3)
C(8)-C(9)	1.512(4)	N-C(7)-C(6)	116.9(3)
C(9)-C(11)	1.485(5)	N-C(8)-C(16)	111.7(3)
C(9)-C(10)	1.498(5)	N-C(8)-C(9)	109.7(3)
C(10)-C(11)	1.493(6)	C(16)-C(8)-C(9)	112.1(3)
C(11)-C(12)	1.509(5)	C(11)-C(9)-C(10)	60.1(2)
C(12)-C(13)	1.476(7)	C(11)-C(9)-C(8)	120.4(3)
C(13)-C(14)	1.553(8)	C(10)-C(9)-C(8)	118.8(3)
C(14)-C(15)	1.293(8)	C(11)-C(10)-C(9)	59.5(2)
C(16)-C(17)	1.389(4)	C(9)-C(11)-C(10)	60.4(2)
C(16)-C(21)	1.394(4)	C(9)-C(11)-C(12)	120.6(3)
C(17)-C(18)	1.379(5)	C(10)-C(11)-C(12)	122.1(4)
C(18)-C(19)	1.386(5)	C(13)-C(12)-C(11)	113.7(4)
C(19)-C(20)	1.369(5)	C(12)-C(13)-C(14)	112.0(6)
C(20)-C(21)	1.377(4)	C(15)-C(14)-C(13)	118.1(7)
		C(17)-C(16)-C(21)	118.0(3)
		C(17)-C(16)-C(8)	121.2(3)
		C(21)-C(16)-C(8)	120.8(3)
		C(18)-C(17)-C(16)	120.9(3)
		C(17)-C(18)-C(19)	120.4(3)
		C(20)-C(19)-C(18)	119.0(4)
		C(19)-C(20)-C(21)	121.1(3)
		C(20)-C(21)-C(16)	120.6(3)

Appendix B, Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for ck102s. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2(a^*)^2U^{11} + ... + 2hk(a^*)(b^*)U^{12}]$.

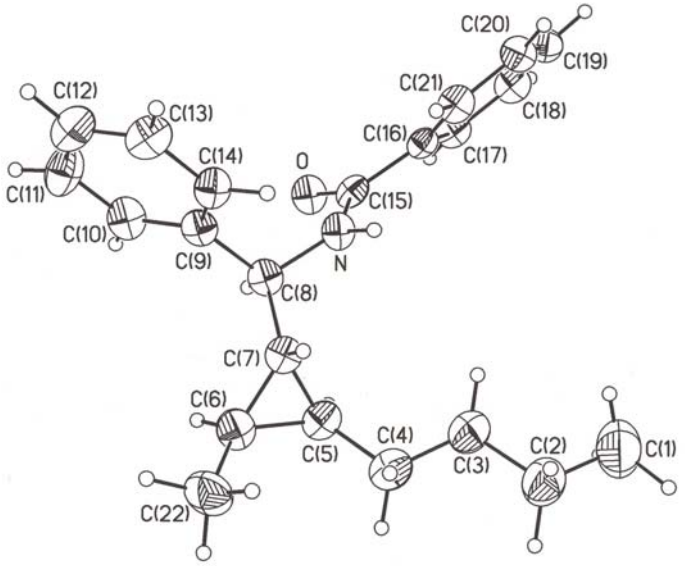
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O	18(1)	44(1)	41(1)	-2(1)	-4(1)	-4(1)
N	17(1)	33(2)	39(2)	-3(1)	-5(1)	-2(1)
C(1)	23(2)	31(2)	32(2)	-4(2)	-4(1)	4(1)
C(2)	26(2)	44(2)	33(2)	-9(2)	-1(2)	-2(2)
C(3)	36(2)	34(2)	34(2)	3(2)	-10(2)	-5(2)
C(4)	34(2)	34(2)	45(2)	-4(2)	-12(2)	6(2)
C(5)	21(2)	33(2)	42(2)	-6(2)	-6(2)	1(1)
C(6)	19(2)	28(2)	29(2)	-10(2)	-4(1)	-2(1)
C(7)	21(2)	29(2)	35(2)	-14(2)	-4(1)	-1(1)
C(8)	20(2)	36(2)	29(2)	-1(2)	-2(1)	0(1)
C(9)	27(2)	45(2)	30(2)	-7(2)	-1(2)	1(2)
C(10)	76(3)	77(3)	47(3)	3(2)	-13(2)	-30(3)
C(11)	38(2)	78(3)	43(2)	-31(2)	3(2)	-8(2)
C(12)	51(3)	106(4)	60(3)	-52(3)	8(2)	-21(3)
C(13)	79(4)	59(4)	266(9)	-45(5)	-77(5)	-3(3)
C(14)	103(6)	81(5)	367(14)	-89(7)	-41(7)	-5(4)
C(15)	144(7)	134(7)	196(8)	-59(6)	-24(6)	-18(6)
C(16)	20(2)	33(2)	32(2)	-5(2)	-6(1)	3(1)
C(17)	22(2)	44(2)	52(2)	-4(2)	-9(2)	-2(2)
C(18)	34(2)	37(2)	78(3)	-8(2)	-15(2)	-8(2)
C(19)	36(2)	39(2)	83(3)	-23(2)	-19(2)	7(2)
C(20)	26(2)	49(2)	52(2)	-21(2)	-12(2)	4(2)
C(21)	24(2)	37(2)	41(2)	-7(2)	-7(2)	-1(2)

Appendix B, Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for ck102s.

	x	y	z	U(eq)
H(1N)	2790(70)	270(30)	3136(19)	50(11)
H(1A)	2000	-188	4358	35
H(2A)	1175	-1870	5417	41
H(3A)	4163	-3668	5699	42
H(4A)	7996	-3788	4896	45
H(5A)	8871	-2095	3861	38
H(8A)	6461	1851	2139	35
H(9A)	1164	1651	1920	41
H(10A)	2396	2797	671	80
H(10B)	5350	2935	870	80
H(11A)	5769	443	1159	62
H(12A)	521	263	902	83
H(12B)	2810	-212	309	83
H(13A)	1590	-1550	1805	153
H(13B)	3989	-2000	1241	153
H(14A)	-1171	-2545	1206	213
H(14B)	424	-2195	394	213
H(15A)	78	-4399	679	231
H(15B)	1243	-4350	1457	231
H(15C)	2967	-3984	663	231
H(17A)	7440	4208	2189	47
H(18A)	6648	6372	2659	59
H(19A)	2857	6795	3426	61
H(20A)	-117	5040	3697	48
H(21A)	630	2879	3229	40

Appendix C

X-ray Structure and Data of a Derivative of Cyclopropane 267.



Appendix C, Table 1. Crystal data and structure refinement for ck502s.

Identification code	ck502s	
Empirical formula	$C_{22}H_{27}NO$	
Formula weight	321.45	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 5.3816(6) Å	α = 98.396(2)°
	b = 10.2141(11) Å	β = 96.477(2)°
	c = 17.2013(19) Å	γ = 94.354(2)°
Volume	925.31(18) $Å^3$	
Z	2	
Density (calculated)	1.154 Mg/m^3	
Absorption coefficient	0.070 mm^{-1}	
F(000)	348	
Crystal size	0.29 x 0.03 x 0.03 mm^3	
Theta range for data collection	2.02 to 25.00°	
Index ranges	$-6 \le h \le 6, -12 \le k \le 12, -20 \le l \le 20$	
Reflections collected	7446	
Independent reflections	3268 [R(int) = 0.0545]	
Completeness to theta = 25.00°	100.0%	
Absorption correction	Sadabs	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3268 / 0 / 325	
Goodness-of-fit on F^2	1.036	
Final R indices [I>2sigma(I)]	R1 = 0.0743, wR2 = 0.1549	
R indices (all data)	R1 = 0.1263, wR2 = 0.1713	
Largest diff. peak and hole	0.280 and -0.167 $e.Å^{-3}$	

Appendix C, Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for ck502s. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O	3321(4)	5849(2)	1936(1)	38(1)
N	7560(5)	6105(3)	2092(2)	32(1)
C(1)	12461(13)	1826(6)	3554(4)	92(2)
C(2)	13152(9)	3254(5)	3954(3)	69(1)
C(3)	11184(8)	4172(4)	3713(3)	59(1)
C(4)	11701(7)	5569(4)	4179(2)	48(1)
C(5)	9688(7)	6423(3)	3939(2)	41(1)
C(6)	9965(7)	7915(4)	4142(2)	44(1)
C(7)	9965(6)	7261(3)	3309(2)	32(1)
C(8)	7811(6)	7311(3)	2681(2)	34(1)
C(9)	8037(5)	8546(3)	2288(2)	33(1)
C(10)	6417(6)	9519(3)	2398(2)	42(1)
C(11)	6623(7)	10634(4)	2029(2)	51(1)
C(12)	8443(6)	10776(4)	1539(2)	47(1)
C(13)	10084(7)	9814(3)	1432(2)	44(1)
C(14)	9897(6)	8707(3)	1800(2)	36(1)
C(15)	5326(5)	5481(3)	1745(2)	30(1)
C(16)	5411(5)	4349(3)	1101(2)	29(1)
C(17)	3435(6)	3339(3)	961(2)	33(1)
C(18)	3328(6)	2323(3)	337(2)	39(1)
C(19)	5169(6)	2284(3)	-156(2)	36(1)
C(20)	7137(6)	3264(3)	-22(2)	36(1)
C(21)	7267(6)	4274(3)	601(2)	34(1)
C(22)	12291(8)	8665(5)	4628(3)	62(1)

Appendix C, Table 3. Bond lengths [Å] and angles [°] for ck502s.

O-C(15)	1.233(3)	C(15)-N-C(8)	123.4(3)	N-C(8)-H(8)	105.3(15)
N-C(15)	1.349(4)	C(15)-N-H(1N)	117(2)	C(7)-C(8)-H(8)	110.9(16)
N-C(8)	1.462(4)	C(8)-N-H(1N)	120(2)	C(9)-C(8)-H(8)	106.5(16)
N-H(1N)	0.84(3)	C(2)-C(1)-H(1A)	104(2)	C(10)-C(9)-C(14)	118.6(3)
C(1)-C(2)	1.519(7)	C(2)-C(1)-H(1B)	86(4)	C(10)-C(9)-C(8)	121.3(3)
C(1)-H(1A)	1.09(5)	H(1A)-C(1)-H(1B)	114(5)	C(14)-C(9)-C(8)	120.0(3)
C(1)-H(1B)	1.09(8)	C(2)-C(1)-H(1C)	100(3)	C(9)-C(10)-C(11)	120.8(4)
C(1)-H(1C)	1.09(6)	H(1A)-C(1)-H(1C)	119(4)	C(9)-C(10)-H(10)	122.7(19)
C(2)-C(3)	1.529(6)	H(1B)-C(1)-H(1C)	123(5)	C(11)-C(10)-H(10)	116.5(19)
C(2)-H(2A)	1.13(8)	C(1)-C(2)-C(3)	112.1(4)	C(12)-C(11)-C(10)	120.2(4)
C(2)-H(2B)	1.15(7)	C(1)-C(2)-H(2A)	108(4)	C(12)-C(11)-H(11)	123(2)
C(3)-C(4)	1.519(5)	C(3)-C(2)-H(2A)	109(4)	C(10)-C(11)-H(11)	117(2)
C(3)-H(3A)	1.00(3)	C(1)-C(2)-H(2B)	107(3)	C(11)-C(12)-C(13)	119.4(4)
C(3)-H(3B)	1.08(5)	C(3)-C(2)-H(2B)	100(3)	C(11)-C(12)-H(12)	118(2)
C(4)-C(5)	1.501(5)	H(2A)-C(2)-H(2B)	121(5)	C(13)-C(12)-H(12)	123(2)
C(4)-H(4A)	0.98(3)	C(4)-C(3)-C(2)	112.6(3)	C(14)-C(13)-C(12)	120.8(4)
C(4)-H(4B)	1.08(4)	C(4)-C(3)-H(3A)	114.3(17)	C(14)-C(13)-H(13)	120(2)
C(5)-C(7)	1.490(5)	C(2)-C(3)-H(3A)	108.8(18)	C(12)-C(13)-H(13)	119(2)
C(5)-C(6)	1.505(5)	C(4)-C(3)-H(3B)	120(3)	C(13)-C(14)-C(9)	120.2(3)
C(5)-H(5)	0.96(3)	C(2)-C(3)-H(3B)	104(3)	C(13)-C(14)-H(14)	120.9(19)
C(6)-C(7)	1.490(5)	H(3A)-C(3)-H(3B)	96(3)	C(9)-C(14)-H(14)	118.8(19)
C(6)-C(22)	1.511(5)	C(5)-C(4)-C(3)	110.7(3)	O-C(15)-N	121.9(3)
C(6)-H(6)	0.94(3)	C(5)-C(4)-H(4A)	110(2)	O-C(15)-C(16)	121.8(3)
C(7)-C(8)	1.502(4)	C(3)-C(4)-H(4A)	109(2)	N-C(15)-C(16)	116.3(3)
C(7)-H(7)	0.92(3)	C(5)-C(4)-H(4B)	104.6(19)	C(21)-C(16)-C(17)	118.1(3)
C(8)-C(9)	1.518(4)	C(3)-C(4)-H(4B)	112.1(19)	C(21)-C(16)-C(15)	123.7(3)
C(8)-H(8)	0.96(3)	H(4A)-C(4)-H(4B)	111(3)	C(17)-C(16)-C(15)	118.1(3)
C(9)-C(10)	1.378(4)	C(7)-C(5)-C(4)	121.2(3)	C(18)-C(17)-C(16)	120.5(3)
C(9)-C(14)	1.393(4)	C(7)-C(5)-C(6)	59.7(2)	C(18)-C(17)-H(17)	124.7(17)
C(10)-C(11)	1.386(5)	C(4)-C(5)-C(6)	123.2(3)	C(16)-C(17)-H(17)	114.8(17)
C(10)-H(10)	0.94(3)	C(7)-C(5)-H(5)	111(2)	C(17)-C(18)-C(19)	120.3(3)
C(11)-C(12)	1.374(5)	C(4)-C(5)-H(5)	114(2)	C(17)-C(18)-H(18)	120(2)
C(11)-H(11)	0.95(4)	C(6)-C(5)-H(5)	116(2)	C(19)-C(18)-H(18)	120(2)
C(12)-C(13)	1.377(5)	C(7)-C(6)-C(5)	59.7(2)	C(18)-C(19)-C(20)	119.9(3)
C(12)-H(12)	0.93(4)	C(7)-C(6)-C(22)	122.3(3)	C(18)-C(19)-H(19)	119.2(16)
C(13)-C(14)	1.376(5)	C(5)-C(6)-C(22)	121.9(3)	C(20)-C(19)-H(19)	120.8(17)
C(13)-H(13)	0.91(4)	C(7)-C(6)-H(6)	113.3(19)	C(21)-C(20)-C(19)	120.1(3)
C(14)-H(14)	0.95(3)	C(5)-C(6)-H(6)	116.9(18)	C(21)-C(20)-H(20)	121.1(18)
C(15)-C(16)	1.487(4)	C(22)-C(6)-H(6)	112.9(18)	C(19)-C(20)-H(20)	118.7(18)
C(16)-C(21)	1.389(4)	C(5)-C(7)-C(6)	60.7(2)	C(20)-C(21)-C(16)	121.1(3)
C(16)-C(17)	1.399(4)	C(5)-C(7)-C(8)	120.5(3)	C(20)-C(21)-H(21)	118.4(17)
C(17)-C(18)	1.373(5)	C(6)-C(7)-C(8)	121.6(3)	C(16)-C(21)-H(21)	120.5(17)
C(17)-H(17)	0.98(3)	C(5)-C(7)-H(7)	113.0(17)	C(6)-C(22)-H(22A)	105.8(19)
C(18)-C(19)	1.375(5)	C(6)-C(7)-H(7)	114.8(16)	C(6)-C(22)-H(22B)	112(3)
C(18)-H(18)	0.96(3)	C(8)-C(7)-H(7)	115.2(17)	H(22A)-C(22)-H(22B)	113(3)
C(19)-C(20)	1.375(4)	N-C(8)-C(7)	109.8(3)	C(6)-C(22)-H(22C)	111(3)
C(19)-H(19)	0.92(3)	N-C(8)-C(9)	110.9(3)	H(22A)-C(22)-H(22C)	107(3)
C(20)-C(21)	1.367(4)	C(7)-C(8)-C(9)	113.1(3)	H(22B)-C(22)-H(22C)	107(4)
C(20)-H(20)	0.93(3)				
C(21)-H(21)	0.94(3)				
C(22)-H(22A)	1.02(3)				
C(22)-H(22B)	1.05(5)				
C(22)-H(22C)	1.09(5)				

Appendix C, Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for ck502s. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2(a^*)^2U^{11} + ... + 2hk(a^*)(b^*)U^{12}]$.

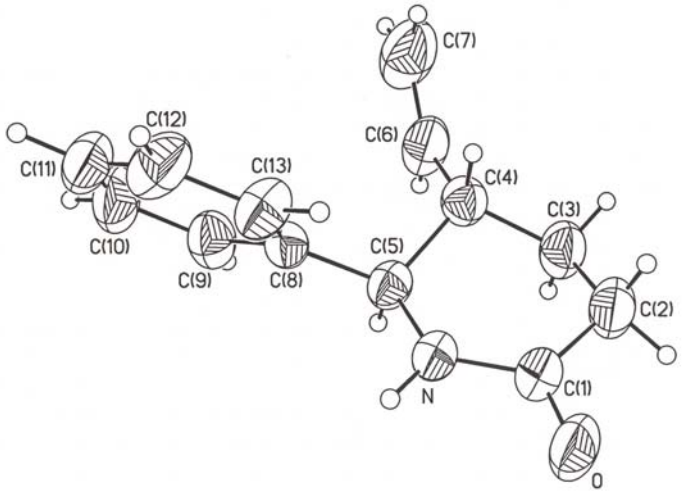
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O	20(1)	41(1)	52(1)	3(1)	5(1)	0(1)
N	18(1)	33(2)	44(2)	3(1)	3(1)	0(1)
C(1)	94(4)	70(4)	105(5)	-4(3)	0(4)	24(3)
C(2)	63(3)	63(3)	78(3)	4(3)	-8(3)	17(2)
C(3)	56(3)	59(3)	60(3)	9(2)	-3(2)	15(2)
C(4)	43(2)	49(2)	52(3)	16(2)	5(2)	0(2)
C(5)	30(2)	43(2)	50(2)	12(2)	2(2)	-1(2)
C(6)	35(2)	45(2)	50(2)	3(2)	5(2)	4(2)
C(7)	21(2)	37(2)	39(2)	7(2)	7(2)	0(1)
C(8)	25(2)	36(2)	40(2)	3(2)	4(2)	-1(1)
C(9)	20(2)	36(2)	39(2)	0(2)	-4(1)	-2(1)
C(10)	26(2)	45(2)	55(2)	3(2)	6(2)	1(2)
C(11)	31(2)	42(2)	80(3)	16(2)	0(2)	7(2)
C(12)	33(2)	43(2)	63(3)	17(2)	-11(2)	-10(2)
C(13)	29(2)	48(2)	53(2)	15(2)	-1(2)	-8(2)
C(14)	24(2)	36(2)	47(2)	6(2)	2(2)	3(2)
C(15)	23(2)	29(2)	39(2)	14(2)	3(1)	-3(1)
C(16)	22(2)	28(2)	34(2)	7(1)	-6(1)	-2(1)
C(17)	24(2)	37(2)	39(2)	11(2)	0(2)	-2(1)
C(18)	28(2)	37(2)	48(2)	8(2)	-1(2)	-8(2)
C(19)	32(2)	37(2)	37(2)	2(2)	-6(2)	2(2)
C(20)	28(2)	42(2)	38(2)	5(2)	5(2)	2(2)
C(21)	20(2)	34(2)	46(2)	9(2)	2(2)	-6(1)
C(22)	53(3)	62(3)	60(3)	-6(2)	-11(2)	-1(2)

Appendix C, Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for ck502s.

	x	y	z	U(eq)
H(1N)	8850(60)	5770(30)	1960(17)	29(9)
H(1A)	14070(100)	1320(50)	3750(30)	107(16)
H(1B)	12600(130)	2210(70)	3000(50)	190(30)
H(1C)	10680(130)	1620(60)	3780(40)	160(30)
H(2A)	13290(130)	3270(70)	4610(50)	200(30)
H(2B)	14820(120)	3660(60)	3670(40)	170(30)
H(3A)	11020(50)	4130(30)	3120(20)	38(9)
H(3B)	9410(100)	3610(50)	3720(30)	130(19)
H(4A)	13330(70)	5950(30)	4080(20)	55(11)
H(4B)	11650(60)	5580(30)	4800(20)	63(11)
H(5)	8010(60)	6000(30)	3886(19)	50(10)
H(6)	8500(60)	8330(30)	4224(18)	35(9)
H(7)	11530(50)	7260(20)	3135(15)	22(7)
H(8)	6250(50)	7310(20)	2901(16)	22(7)
H(10)	5180(60)	9490(30)	2741(19)	38(9)
H(11)	5530(70)	11300(40)	2150(20)	76(13)
H(12)	8460(70)	11510(40)	1280(20)	62(12)
H(13)	11320(70)	9920(30)	1120(20)	54(11)
H(14)	10980(60)	8020(30)	1710(18)	41(9)
H(17)	2180(60)	3440(30)	1328(18)	40(9)
H(18)	1940(60)	1640(30)	240(20)	53(10)
H(19)	5020(50)	1620(30)	-590(16)	20(7)
H(20)	8380(60)	3210(30)	-359(18)	32(8)
H(21)	8630(50)	4920(30)	681(16)	24(7)
H(22A)	13770(70)	8250(30)	4410(20)	51(10)
H(22B)	12290(80)	8640(40)	5240(30)	99(16)
H(22C)	12450(90)	9710(50)	4550(30)	126(19)

Appendix D

X-ray Structure and Data of Lactam *anti*-287



Appendix D, Table 1. Crystal data and structure refinement for chris601.

Identification code	chris601	
Empirical formula	$C_{13}H_{15}NO$	
Formula weight	201.26	
Temperature	210(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 12.024(2) Å	α = 90°
	b = 6.1680(12) Å	β = 96.28(3)°
	c = 15.437(3) Å	γ = 90°
Volume	1138.0(4) $Å^3$	
Z	4	
Density (calculated)	1.175 Mg/m^3	
Absorption coefficient	0.074 mm^{-1}	
F(000)	432	
Crystal size	0.35 x 0.14 x 0.04 mm^3	
Theta range for data collection	2.65 to 25.03°	
Index ranges	$0 \le h \le 14$, $0 \le k \le 7$, $-18 \le l \le 18$	
Reflections collected	2119	
Independent reflections	2016 [R(int) = 0.0341]	
Completeness to theta = 25.03°	100.0%	
Absorption correction	Sadabs	
Max. and min. transmission	0.9970 and 0.9745	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2016 / 0 / 197	
Goodness-of-fit on F^2	1.055	
Final R indices [I>2sigma(I)]	R1 = 0.0500, wR2 = 0.0886	
R indices (all data)	R1 = 0.1103, wR2 = 0.1077	
Extinction coefficient	0.017(3)	
Largest diff. peak and hole	0.111 and -0.118 $e.Å^{-3}$	

Appendix D, Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for chris601. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O	10119(2)	84(3)	11145(1)	66(1)
N	9090(2)	2373(3)	10251(1)	45(1)
C(1)	9491(2)	1678(4)	11045(1)	47(1)
C(2)	9136(3)	2849(5)	11820(2)	58(1)
C(3)	8558(3)	4990(5)	11625(2)	56(1)
C(4)	7729(2)	4854(4)	10802(1)	45(1)
C(5)	8389(2)	4283(4)	10038(1)	41(1)
C(6)	7111(3)	6958(5)	10638(2)	61(1)
C(7)	6028(4)	7211(9)	10602(2)	92(1)
C(8)	7645(2)	3901(4)	9195(1)	40(1)
C(9)	7470(2)	5552(5)	8586(2)	55(1)
C(10)	6756(3)	5232(6)	7824(2)	70(1)
C(11)	6234(2)	3296(6)	7667(2)	71(1)
C(12)	6404(2)	1640(6)	8256(2)	69(1)
C(13)	7110(2)	1955(4)	9018(2)	55(1)

Appendix D, Table 3. Bond lengths [Å] and angles [°] for chris601.

O-C(1)	1.239(3)	C(1)-N-C(5)	127.2(2)	N-C(5)-H(5)	110.2(11)
N-C(1)	1.338(3)	C(1)-N-H(1N)	113.7(16)	C(8)-C(5)-H(5)	106.7(12)
N-C(5)	1.465(3)	C(5)-N-H(1N)	119.0(16)	C(4)-C(5)-H(5)	106.8(12)
N-H(1N)	0.90(3)	O-C(1)-N	121.5(2)	C(7)-C(6)-C(4)	125.6(4)
C(1)-C(2)	1.498(3)	O-C(1)-C(2)	120.4(2)	C(7)-C(6)-H(6)	121.0(18)
C(2)-C(3)	1.507(4)	N-C(1)-C(2)	118.1(2)	C(4)-C(6)-H(6)	113.3(18)
C(2)-H(2A)	0.92(3)	C(1)-C(2)-C(3)	115.4(2)	C(6)-C(7)-H(7A)	123(2)
C(2)-H(2B)	1.00(3)	C(1)-C(2)-H(2A)	104.5(18)	C(6)-C(7)-H(7B)	113.7(19)
C(3)-C(4)	1.528(3)	C(3)-C(2)-H(2A)	111.5(18)	H(7A)-C(7)-H(7B)	123(3)
C(3)-H(3A)	0.96(2)	C(1)-C(2)-H(2B)	107.9(16)	C(13)-C(8)-C(9)	118.3(2)
C(3)-H(3B)	0.96(3)	C(3)-C(2)-H(2B)	111.0(16)	C(13)-C(8)-C(5)	121.7(2)
C(4)-C(6)	1.504(3)	H(2A)-C(2)-H(2B)	106(2)	C(9)-C(8)-C(5)	120.0(2)
C(4)-C(5)	1.534(3)	C(2)-C(3)-C(4)	111.2(2)	C(8)-C(9)-C(10)	120.2(3)
C(4)-H(4)	1.00(2)	C(2)-C(3)-H(3A)	113.0(14)	C(8)-C(9)-H(9)	120.5(15)
C(5)-C(8)	1.514(3)	C(4)-C(3)-H(3A)	107.0(14)	C(10)-C(9)-H(9)	119.3(15)
C(5)-H(5)	1.01(2)	C(2)-C(3)-H(3B)	109.4(15)	C(11)-C(10)-C(9)	120.3(3)
C(6)-C(7)	1.306(4)	C(4)-C(3)-H(3B)	110.5(14)	C(11)-C(10)-H(10)	121.7(17)
C(6)-H(6)	0.97(3)	H(3A)-C(3)-H(3B)	106(2)	C(9)-C(10)-H(10)	117.9(18)
C(7)-H(7A)	0.97(3)	C(6)-C(4)-C(3)	111.0(2)	C(10)-C(11)-C(12)	120.3(3)
C(7)-H(7B)	1.01(3)	C(6)-C(4)-C(5)	110.9(2)	C(10)-C(11)-H(11)	122.1(18)
C(8)-C(13)	1.375(3)	C(3)-C(4)-C(5)	107.9(2)	C(12)-C(11)-H(11)	117.6(18)
C(8)-C(9)	1.386(3)	C(6)-C(4)-H(4)	109.3(11)	C(11)-C(12)-C(13)	119.5(3)
C(9)-C(10)	1.393(4)	C(3)-C(4)-H(4)	110.2(12)	C(11)-C(12)-H(12)	122.6(14)
C(9)-H(9)	1.00(3)	C(5)-C(4)-H(4)	107.5(12)	C(13)-C(12)-H(12)	117.9(14)
C(10)-C(11)	1.359(4)	N-C(5)-C(8)	109.85(19)	C(8)-C(13)-C(12)	121.4(3)
C(10)-H(10)	0.98(3)	N-C(5)-C(4)	110.13(18)	C(8)-C(13)-H(13)	119.8(15)
C(11)-C(12)	1.368(4)	C(8)-C(5)-C(4)	112.99(19)	C(12)-C(13)-H(13)	118.9(15)
C(11)-H(11)	0.95(3)				
C(12)-C(13)	1.386(3)				
C(12)-H(12)	1.01(3)				
C(13)-H(13)	0.97(3)				

Appendix D, Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for chris601. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2(a^*)^2U^{11} + ... + 2hk(a^*)(b^*)U^{12}]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O	73(1)	78(1)	45(1)	7(1)	-6(1)	33(1)
N	42(1)	58(1)	36(1)	2(1)	0(1)	10(1)
C(1)	43(1)	57(2)	40(1)	4(1)	-2(1)	2(1)
C(2)	65(2)	68(2)	39(2)	3(1)	-2(1)	12(2)
C(3)	63(2)	61(2)	41(2)	-4(1)	-2(1)	8(2)
C(4)	47(1)	47(2)	40(1)	-3(1)	3(1)	1(1)
C(5)	41(1)	41(1)	40(1)	5(1)	-1(1)	1(1)
C(6)	69(2)	66(2)	46(2)	-5(1)	-7(1)	17(2)
C(7)	91(3)	113(3)	68(2)	-14(2)	-10(2)	46(3)
C(8)	40(1)	45(1)	35(1)	3(1)	5(1)	4(1)
C(9)	65(2)	56(2)	43(2)	6(1)	4(1)	6(2)
C(10)	81(2)	84(2)	43(2)	10(2)	-4(2)	20(2)
C(11)	57(2)	100(3)	50(2)	-14(2)	-13(1)	22(2)
C(12)	58(2)	71(2)	72(2)	-12(2)	-14(2)	-2(2)
C(13)	53(2)	54(2)	56(2)	7(1)	-8(1)	0(1)

Appendix D, Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for chris601.

	x	y	z	U(eq)
H(1N)	9320(20)	1570(40)	9814(17)	70(9)
H(2A)	8680(20)	1890(40)	12063(18)	80(10)
H(2B)	9810(20)	3030(40)	12251(18)	91(9)
H(3A)	9070(19)	6150(40)	11537(15)	57(8)
H(3B)	8182(19)	5420(40)	12115(17)	66(8)
H(4)	7178(17)	3660(30)	10859(13)	40(6)
H(5)	8870(17)	5580(30)	9938(13)	45(6)
H(6)	7600(20)	8190(50)	10597(18)	93(11)
H(7A)	5660(30)	8600(50)	10490(20)	109(12)
H(7B)	5600(30)	5810(60)	10660(20)	113(14)
H(9)	7830(20)	6990(40)	8699(16)	74(9)
H(10)	6660(20)	6430(50)	7403(19)	95(10)
H(11)	5750(20)	3030(50)	7150(19)	91(9)
H(12)	6040(20)	170(40)	8157(15)	74(8)
H(13)	7222(19)	780(40)	9431(16)	69(8)

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