NOVEL CASCADE REACTIONS OF ALKENYLZIRCONOCENES AND THEIR APPLICATION TO THE SYNTHESIS OF CYCLOPROPYL PEPTIDE MIMETICS

by

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Abstract

NOVEL CASCADE REACTIONS OF ALKENYLZIRCONOCENES AND THEIR APPLICATION TO THE SYNTHESIS OF CYCLOPROPYL PEPTIDE MIMETICS

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We have successfully applied the Zr→Zn methodology developed in the Wipf group to the preparation of functionalized allylic amides and alcohols via the 1,2-addition to imines and α-keto esters. During the preparation of allylic amides, concomitant formation of *C*-cyclopropylalkylamides was observed in CH_2Cl_2. The combination of the Zr→Zn methodology with the Simmons-Smith cyclopropanation reaction has led to the discovery of a novel cascade reaction for the preparation of *C*,*C*-dicyclopropylmethylamides from simple, readily available starting materials. These functionalized amides have served as precursors in a diversity-oriented approach for the preparation of 7-, 8-, and 9-membered azaspirocyclic ring structures based on reductive amination, epoxide opening or ring-closing metathesis strategies.

Finally, a small library of α,β-cyclopropyl-γ-amino acids was prepared in 6-7 steps from readily available starting materials and evaluated for their potential as peptide mimetics. Simple amide derivatives were found to adopt stable sheet-like structures in the solid state, whereas the structural properties of oligopeptides were not readily assessed using crystallographic techniques. A combination of molecular modeling, circular dichroism and NMR studies was used to ascertain the solution folding preferences of our novel peptide mimetics.

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I would like to thank my research advisor, Professor Peter Wipf, for his guidance and patience during my Ph.D studies. His dedication to academic excellence and his students is a standard to which we should all aspire. I would like to extend my appreciation to Professors Floreancig, Mokotoff, Nelson and Wilcox for their encouragement and helpful discussions concerning my proposal examination and dissertation studies. I have had the privilege to share my time in the Wipf group with an outstanding group of colleagues who have been a source of endless encouragement and knowledge. In particular, I would like to thank some of my former lab mates, Drs. Andy Phillips, Kazuo Okumura, Jon Reeves and Sonia Rodriguez as well for all their help. Finally, I would like to express my heartfelt appreciation to Michelle Woodring for all that she has done for me during the past six years, particularly through the tough times. I would like to thank Dr. Steven Geib for x-ray diffraction analysis, Jingbo Xiao and Drs. Fu-Tyan and Fu-Mei Lin for assistance with high-field NMR spectroscopy, Dr. Kasi Somayajula for mass spectral analysis and the University of Pittsburgh for financial support. Finally, without my parent's continual encouragement and support, none of what has been accomplished would be possible.

List of Abbreviations

Ac .....acetyl
Bn .....benzyl
BOP .....benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
Bu .....butyl
Bz .....benzoyl
COD 1,5-cyclooctadiene
Cp .....cyclopentadienyl
Cy .....cyclohexyl
DBU .....1,8-diazobicyclo[5.4.0]undec-7-ene
DCC .....dicyclohexylcarbodiimide
DEAD .....diethylazodicarboxylate
DIPEA .....diisopropylethylamine
DMAP 4-dimethylaminopyridine
DME 1,2-dimethoxyethane
DMF .....*N*,*N*-dimethylformamide
DMSO .....methyl sulfoxide
DPPA .....diphenylphosphoryl azide
EDCI .....*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide
Fmoc 9-fluorenylmethoxycarbonyl
HMDS .....hexamethyldisilazane
HMPA .....hexamethylphosphoramide
hPXR .....human Pregnane X receptor
Imid .....imidazole
m-CPBA .....3-chloroperoxybenzoic acid
mPXR .....murine Pregnane X receptor
Ms .....methanesulfonyl
PDC .....pyridinium dichromate
PG .....protective group
Ph .....phenyl
Phg .....phenylglycine
Pr .....propyl
TAc .....trichloroacetyl
TBAF .....tetra-*n*-butylammonium fluoride
TBS .....*tert*-butyldimethylsilyl
TES .....triethylsilyl
Tf .....trifluoromethanesulfonyl
THF .....tetrahydrofuran
TIPS .....triisopropylsilyl
TMPDA .....*N*,*N*,*N*',*N*'-tetramethylpropylenediamine
TMS .....trimethylsilyl
Tol .....*p*-tolyl
Ts .....*p*-toluenesulfonyl
μW .....microwave irradiation

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1.0 New Reaction Manifolds in the Chemistry of Alkenylzirconocenes

1.1 Introduction

1.1.1 Preparation and Use of Alkenylzirconocenes

The development of organozirconium compounds as useful reactive intermediates for synthetic organic and inorganic chemists was sparked nearly two decades after the synthesis of the first zirconocene, Cp_2ZrBr_2,[1] by the preparation of zirconocene hydrides[2] in the early 1970's. These complexes have found broad use in synthetic organic and polymer chemistry. Shortly after the discovery of zirconocene hydrochloride, Schwartz and co-workers pioneered its use for the functionalization of alkenes[3] and alkynes[4] via hydrometalation, and the reagent is now commonly known as "Schwartz reagent". Hydrozirconation[5] is a mild method for the preparation of functionalized organometallic compounds from readily available precursors (alkenes and alkynes). Original preparations of Schwartz reagent suffered from contamination with inorganic salts or over-reduced zirconocene dihydride;[2a,6] an improved protocol was introduced by Buchwald and co-workers incorporating a CH_2Cl_2 washing step to convert the dihydride to hydrochloride.[7] While traditional organometallic reagents such as organolithiums

[1] Wilkinson, G.; Pauson, P. L.; Birmingham, J. M.; Cotton, F. A. *J. Am. Chem. Soc.* **1953**, *75*, 1011.
[2] (a) Wailes, P. C.; Weigold, H. *J. Organomet. Chem.* **1970**, *24*, 405. (b) Wailes, P. C.; Weigold, H. *J. Organomet. Chem.* **1970**, *24*, 413.
[3] (a) Wailes, P. C.; Weigold, H. *J. Organomet. Chem.* **1972**, *43*, C32. (b) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115.
[4] (a) Wailes, P. C.; Weigold, H.; Bell, A. P. *J. Organomet. Chem.* **1971**, *27*, 373. (b) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679.
[5] (a) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333. (b) Labinger, J. A. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, p 667. (c) Wipf, P; Jahn, H. *Tetrahedron*, **1996**, *52*, 12853. (d) Wipf, P.; Takahashi, H.; Zhuang, N. *Pure Appl. Chem.* **1998**, *70*, 1077.
[6] (a) Wailes, P. C.; Weigold, H. *Inorg. Synth.* **1979**, *19*, 223. (b) Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1979**, *101*, 3521.
[7] (a) Buchwald, S. L.; La Maire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Tetrahedron Lett.* **1987**, *28*, 3895. (b) Buchwald, S. L.; La Maire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Org. Synth.* **1993**, *71*, 77.

and organomagnesiums suffer from poor functional group compatability, the hydrozirconation of alkynes can be carried out in the presence of ethers, bulky esters (ie, TIPS, *t*-Bu), acyl silanes, and alkenes (with ≤ 1 equiv Cp_2ZrHCl). Despite the inherent polarization of the C-Zr bond (similar to C-Mg of Grignard reagents), their reactivity is comparatively attenuated due to steric shielding of the organometallic bond by the cyclopentadienyl ligands. However, the transmetalation[5c,8] of alkyl- and alkenylzirconocenes has been accomplished with a myriad of metals, including Al,[9] B,[10] Cu,[11] Hg,[12] Ni,[13] Pd,[14] and Sn,[15] thereby allowing for selective transformations of the alkenylorganometallic reagent. For example, upon hydrozirconation of alkynes **1**, the alkenylzironcocenes[16] **2** have been employed as intermediates for the stereoselective introduction of numerous functional groups. Trapping with an electrophilic source of halogens affords vinyl halides **3**;[3,4b,17] reaction with isonitriles **4** followed by mild hydrolysis (aqueous HOAc) affords enals **5**;[18] Pd(0) mediated cross-coupling reactions of halocarbons **6** with or without added $ZnCl_2$ afford trisubstituted olefins **7**;[19,20] activation with

[8] Lipshutz, B. H.; Pfeiffer, S. S.; Tomioka, T.; Noson, K. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002; p 110.

[9] (a) Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 638. (b) Van Horn, D. E.; Negishi, E. *J. Am. Chem. Soc.* **1978**, *100*, 2252. (c) Yoshida, T.; Negishi, E. *J. Am. Chem. Soc.* **1981**, *103*, 4985. (d) Negishi, E.; Boardman, L. D. *Tetrahedron Lett.* **1982**, *23*, 3327. (e) Kondakov, D. Y.; Negishi, E. *J. Am. Chem. Soc.* **1996**, *118*, 1577.

[10] (a) Marselia, J. A.; Caulton, K. G. *J. Am. Chem. Soc.* **1982**, *104*, 2361. (b) Cole, T. E.; Quintanilla, R.; Rodewald, S. *Organometallics* **1991**, *10*, 3777. (c) Cole, T. E.; Rodewald, S.; Watson, C. L. *Tetrahedron Lett.* **1992**, *33*, 5295. (d) Cole, T. E.; Quintanilla, R. *J. Org. Chem.* **1992**, *57*, 7366. (e) Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127.

[11] (a) Yoshifuji, M.; Loots, M. J.; Schwartz, J. *Tetrahedron Lett.* **1977**, *15*, 1303. (b) Wipf, P.; Smitrovich, J. H. *J. Org. Chem.* **1991**, *56*, 6494. (c) Wipf, P.; Smitrovich, J. H.; Moon, C.-W. *J. Org. Chem.* **1992**, *57*, 3178.

[12] Budnik, R. A.; Kochi, J. K. *J. Organomet. Chem.* **1976**, *116*, C3.

[13] (a) Negishi, E.; Van Horn, D. E. *J. Am. Chem. Soc.* **1977**, *99*, 3168. (b) Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254. (c) Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393. (d) Hauske, J. R.; Dorff, P.; Julian, S.; Martinelli, G.; Bussolari, J. *Tetrahedron Lett.* **1992**, *33*, 3715.

[14] (a) Okukado, N.; Van Horn, D. E.; Klima, W. E.; Negishi, E. *Tetrahedron Lett.* **1978**, *16*, 1027. (b) Temple, J. S.; Schwartz, J. *J. Am. Chem. Soc.* **1980**, *102*, 7381. (c) Hayasi, Y.; Riediker, M.; Temple, J. S.; Schwartz, J. *Tetrahedron Lett.* **1981**, *22*, 2629. (d) Barrett, A. G. M.; Pena, M.; Williardson, J. A. *J. Org. Chem.* **1996**, *61*, 1082.

[15] (a) Kim, S.; Kim, K. H. *Tetrahedron Lett.* **1995**, *36*, 3725. (b) Vedejs, E.; Haight, A. R.; Moss, O. *J. Am. Chem. Soc.* **1992**, *114*, 6556.

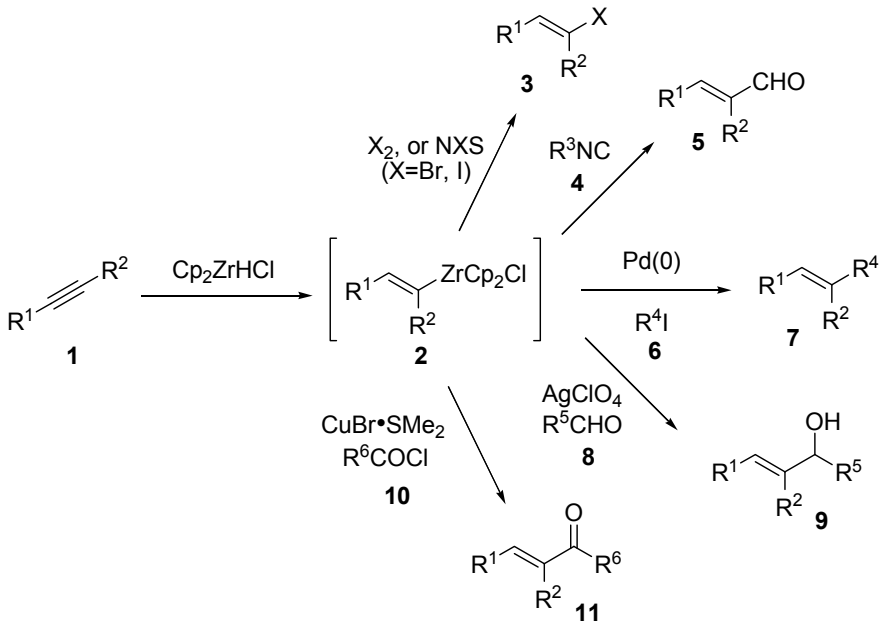
[16] (a) Wipf, P.; Kendall, C. *Chem. Eur. J.* **2002**, *8*, 1778. (b) Wipf, P.; Nunes, R. L. *Tetrahedron* **2004**, *60*, 1269.

[17] For representative examples in total synthesis, see (a) Ragan, J. A.; Nakatsuka, M.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Org. Chem.* **1989**, *54*, 4267. (b) Ireland, R. E.; Highsmith, T. K.; Gegnas, L. D.; Gleason, J. L. *J. Org. Chem.* **1992**, *57*, 5071. (c) Smith, A. B.; Chen, S. S.-Y.; Nelson, F. C.; Reichert, J. M.; Salvatore, B. A. *J. Am. Chem. Soc.* **1995**, *117*, 12013.

[18] (a) Bertolo, C. A.; Schwartz, J. *J. Am. Chem. Soc.* **1976**, *98*, 262. (b) Fryzuk, M. D.; Bates, G. S.; Stone, C. *Tetrahedron Lett.* **1986**, *27*, 1537. (c) Negishi, E.; Swanson, D. R.; Miller, S. R. *Tetrahedron Lett.* **1988**, *29*, 1631. (d) Wipf, P.; Xu, W. *J. Org. Chem.* **1996**, *61*, 6556.

[19] Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254.

Ag(I) salts affords cationic zirconocenes which act as nucleophiles in the addition to aldehydes **8** affording allylic alcohols **9**;[21] and acid chlorides **10** react in the presence of catalytic Cu(I) salts to give enones **11** (Scheme 1.1).[22]

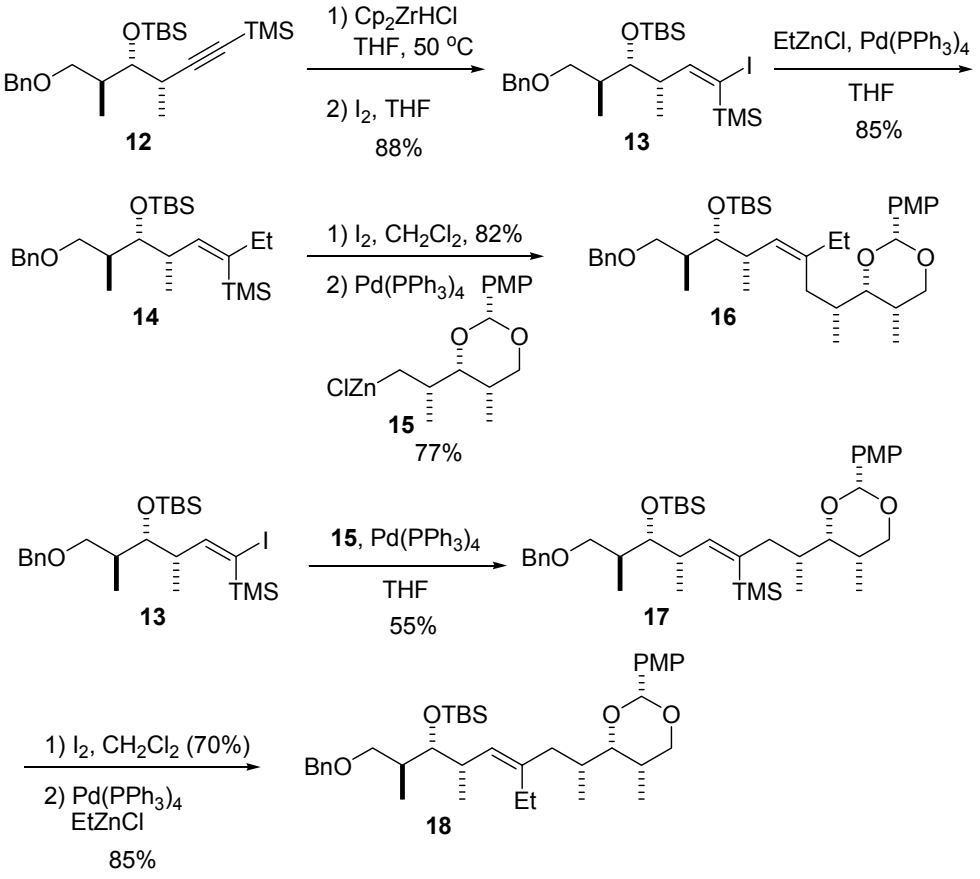


Scheme 1.1. Hydrozirconation-trapping of alkenes and alkynes

One of the most challenging facets of hydrozirconation is the selective hydrometalation of unsymmetrical internal alkynes. Generally, there is preferential hydrozirconation to afford the alkenylzirconocene bearing zirconium at the sterically least demanding position, although sometimes this preference is only modest. Recently, Panek and co-workers have developed a methodology for the stereoselective preparation of *E*- or *Z*-olefins from internal trimethylsilyl-substituted alkynes (Scheme 1.2).[23] Hydrozirconation of alkyne **12** in THF at 50 °C with 2.5 equiv of Cp_2ZrHCl allowed for the thermodynamic equilibration to the least sterically encumbered alkenylzirconocene which is trapped with I_2 to give vinyl iodide **13** in excellent

[20] For Ni-catalyzed coupling of alkenylzirconocenes, see Ni, Y.; Amarasinghe, K. K. D.; Mongomery, J. *Org. Lett.* **2002**, *4*, 1743.
[21] (a) Maeta, H.; Hashimoto, T.; Hasegawa, T.; Suzuki, K. *Tetrahedron Lett.* **1992**, *33*, 5965. (b) Wipf, P.; Xu, W. *J. Org. Chem.* **1993**, *58*, 825.
[22] Wipf, P.; Xu, W. *Synlett* **1992**, 718.
[23] (a) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4914. (b) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912. (c) Arefolov, A.; Langille, N. F.; Panek, J. S. *Org. Lett.* **2001**, *3*, 3281. (d) Langille, N. F.; Panek, J. S. *Org. Lett.* **2004**, *6*, 3203.

yield. Negishi coupling with ethylzinc iodide afforded the trisubstituted alkene **14**. Iododesilylation in CH_2Cl_2 afforded vinyl iodide which was treated under Negishi cross-coupling conditions with the in situ prepared functionalized zinc reagent **15** affording 77% of the functionalized *Z*-trisubstituted alkene **16**, an advanced intermediate for their proposed synthesis of discodermolide. The most interesting feature of this protocol is that the *E*-trisubstituted isomer can be easily prepared simply by reversing the Negishi coupling steps. Coupling of **13** with alkylzinc reagent **15** afforded the intermediate vinylsilane **17** (55%). Iododesilylation (70%) and coupling with ethylzinc iodide afforded the desired *E*-olefin **18** in very good yield.

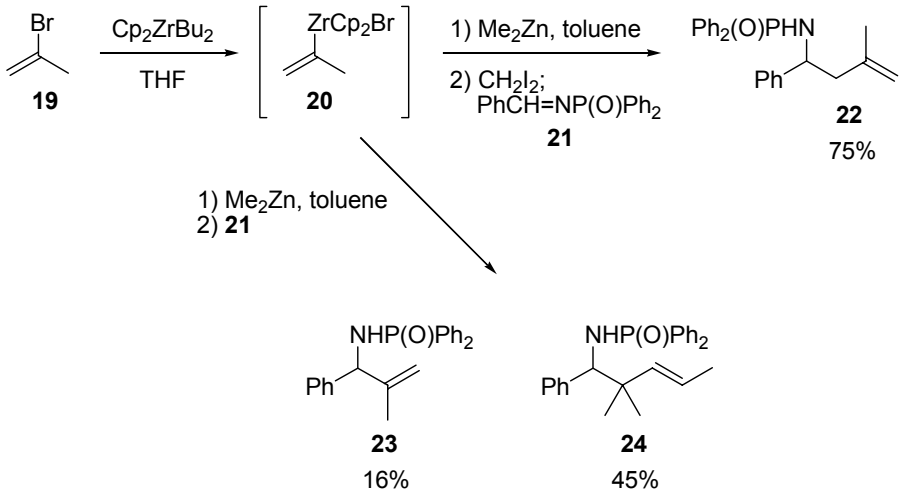


Scheme 1.2. Synthesis of (*E*)- and (*Z*)-trisubstituted olefins via Pd-catalyzed cross-coupling reactions

Alternatively, alkenylzirconocenes have been prepared by the oxidative addition of Cp_2ZrBu_2 (known as the Negishi reagent[24]) into vinyl halides;[25] and Marek and co-workers have

[24] Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829.

extended this methodology to include ethers,[26] sulfonates, sulfides sulfoxides and sulfones.[27] Wipf and Kendall have recently taken advantage of this approach for the preparation of alkenylzirconocenes for the synthesis of allylic and homoallylic amides.[28] Treatment of 2-bromopropene with the Negishi reagent affords the vinylzirconocene **20**. After transmetalation to dimethylzinc, and treatment with CH_2I_2 followed by imine **21**, homoallylic amide **22** is formed in 75% yield. Conversely, if **21** is added directly after Me_2Zn, a mixture of allylic and homoallylic amines **23** and **24** is formed in 61% overall yield.



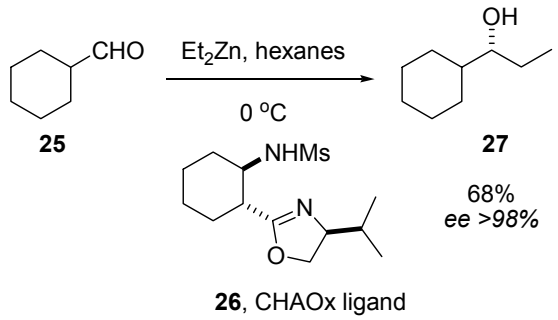
Scheme 1.3. Synthesis of vinylorganometallics by Zr(II) insertion processes

1.1.2 Addition of Organozinc Reagents to Imines and Carbonyl Compounds

The addition of alkylzinc reagents to aldehydes[29] and imines[30] has been widely studied and numerous investigations towards the asymmetric preparation of secondary alcohols and

[25] (a) Takahashi, T.; Kotora, M.; Fischer, R.; Nishihara, Y.; Nakajima, K. *J. Am. Chem. Soc.* **1995**, *117*, 11039. (b) Ichikawa, J.; Fujiwara, M.; Nawata, H.; Okauchi, T.; Minami, T. *Tetrahedron Lett.* **1996**, *37*, 8799. (c) Fujiwara, M.; Ichikawa, J.; Okauchi, T.; Minami, T. *Tetrahedron Lett.* **1999**, *40*, 7261.
[26] Liard, A.; Marek, I. *J. Org. Chem.* **2000**, *65*, 7218.
[27] (a) Farhat, S.; Marek, I. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1410. (b) Farhat, S.; Zouev, I.; Marek, I. *Tetrahedron* **2004**, *60*, 1329.
[28] Wipf, P.; Kendall, C. *Org. Lett.* **2001**, *3*, 2773.
[29] For recent reviews on the catalytic asymmetric organozinc additions to carbonyl compounds, see (a) Noyori, R.; Kitamura, M. *Angew Chem., Int. Ed. Engl.* **1991**, *30*, 49. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (c) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757.
[30] For recent reviews on the asymmetric alkylation of imines, see (a) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

amines have been reported. The majority of ligands or catalysts for the dialkylzinc addition to aldehydes perform poorly when aliphatic aldehydes are used. Wipf and Wang have recently designed a new ligand scaffold, CHAOx, for the enantioselective alkylation of aldehydes with diethylzinc (Scheme 1.4).[31] This ligand, **26**, is particularly effective for the alkylation of aliphatic aldehydes affording optically enriched secondary alcohols with very good to excellent enantioselectivities (*ee* 83-98%) while decreased selectivity was observed for aromatic or α,β-unsaturated aldehydes (*ee* 11-80%). While numerous ligands for the alkylzinc addition to aldehydes have a pronounced non-linear relationship[32] between $ee_{catalyst}$ and $ee_{product}$, the CHAOx ligand has been found to form a monomeric complex with ethylzinc using molecular modeling.[33] This prediction was verified experimentally when a linear relationship between $ee_{catalyst}$ and $ee_{product}$ was observed.

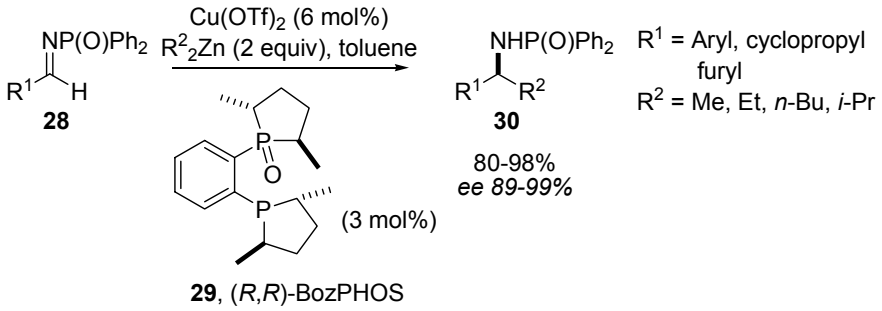


Scheme 1.4. Catalytic asymmetric addition of diethylzinc to aldehydes with the CHAOx ligand **26**

There have been numerous reports in recent years detailing the asymmetric addition of alkylzinc reagents to imines.[34] Analogous to the findings for aldehydes, the addition of alkyl

[31] Wipf, P.; Wang, X. *Org. Lett.* **2002**, *4*, 1197.
[32] (a) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2923. (b) Fenwick, D. R.; Kagan, H. B. *Top. Stereochem.* **1999**, *22*, 257. (c) Heller, D.; Drexler, H.-J.; Fischer, C.; Buschmann, H.; Baumann, W.; Heller, B. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 495. (d) Kagan, H. B. *Synlett* **2001**, 888. (e) Kagan, H. B. *Adv. Synth. Cat.* **2001**, *343*, 227.
[33] Wipf, P.; Pierce, J. G.; Wang, X. *Tetrahedron: Asymmetry* **2003**, *14*, 3605.
[34] (a) Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055. (b) Jimeno, C.; Reddy, K. S.; Sola, L.; Moyano, A.; Pericas, M. A.; Riera, A. *Org. Lett.* **2000**, *2*, 3157. (c) Sato, I.; Kodaka, R.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2912. (d) Pinho, P.; Andersson, P. G. *Tetrahedron* **2001**, *57*, 1615. (e) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 984. (f) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409. (g) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638. (h) Dahmen, S.; Bräse, S. *J. Am. Chem. Soc.* **2002**, *124*, 5940. (i) Zhang, H. L.; Zhang, X. M.; Gong, L. Z.;

zinc reagents to imines does not occur in the absence of either a ligand to activate the zinc reagent or a Lewis acid to activate the imine. Charette and co-workers have recently described their efforts towards the copper-catalyzed asymmetric addition of alkylzinc reagents to *N*-diphenylphosphinoyl imines **28**.[35] In the presence of only 6 mol % $Cu(OTf)_2$ and 3 mol % of the bisphosphine monoxide catalyst **29** (coined (*R*,*R*)-BozPHOS), dialkylzinc reagents (2-3 equiv) can be added to **28** at 0 °C in toluene over 12-36 h, affording the desired secondary phosphinamides **30** in excellent yields and enantioselectivities.[36] Diphosphine catalysts such as Me-DuPHOS can also be used; however in the case of unreactive zinc reagents such as Me_2Zn, a large excess (10 equiv) was required affording low yields and enantioselectivities of **30**.



Scheme 1.5. Catalytic asymmetric addition of dialkylzinc reagents to *N*-diphenylphosphinoyl imines

While Knochel and co-workers have made significant strides towards the preparation of functionalized organozinc reagents,[37] the addition of alkenyl- or alkynylzinc reagents represents a step forward for the preparation of highly valuable allylic and propargylic alcohols and amines.[38,39] The attraction of alkynes as direct precursors for organometallic reagents stems

Mi, A. Q.; Cui, X.; Jiang, Y. Z.; Choi, M. C. K.; Chan, A. S. C. *Org. Lett.* **2002**, 4, 1399. (j) Hermanns, N.; Dahmen, S.; Bolm, C.; Bräse, S. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 3692.

[35] (a) Boezio, A. A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 1692. (b) Boezio, A. A.; Pytkowicz, J.; Côté, A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 14260. (c) Côté, A.; Boezio, A. A.; Charette, A. B. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5405.

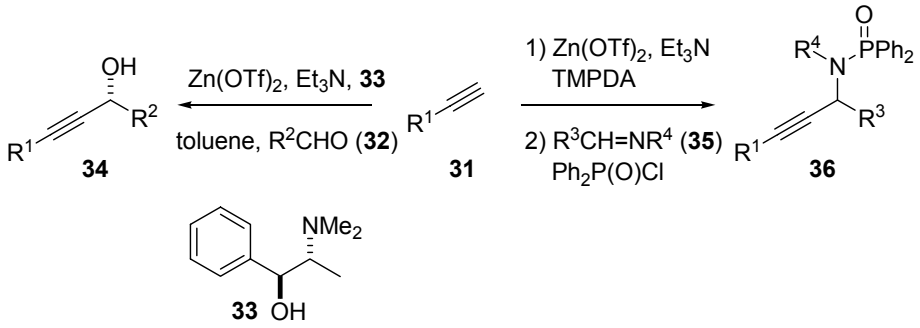
[36] Functionalized diorganozinc reagents prepared according to Knochel's protocol have also been used in this reaction, although $(CuOTf)_2$•PhMe is substituted for $Cu(OTf)_2$.

[37] For reviews on the preparation and use of functionalized organozinc reagents, see (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (b) Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, L. E. *Org. React.* **2001**, *58*, 417.

[38] For representative examples of the addition of alkynylides to aldehydes, see (a) Shahi, S. P.; Koide, K. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 2525.

[39] For representative additions of alkynylides to imines, see (a) Enders, D.; Schankat, J. *Helv. Chim. Acta* **1995**, *78*, 970. (b) Harwood, L. M.; Vines, K. J.; Drew, M. G. B. *Synlett* **1996**, 1051. (c) Brasseur, D.; Marek, I.; Normant, J.-

from their ready availability from commercial sources and bench stability. Recently, it has been demonstrated by Carreira and co-workers that zinc alkynylides can be added to aldehydes and imines under mild conditions to afford propargylic alcohols[40] and amides[41] in excellent yields and, in the case of aldehydes, high enantioselectivity (Scheme 1.6). Treatment of alkyne **31** and aldehyde **32** with Et_3N in the presence of catalytic $Zn(OTf)_2$ and *N*-methylephedrine (**33**) affords the optically enriched propargylic alcohols **34**. This methodology has also been used for the preparation of propargylic amines via the addition of zinc alkynylides (stoichiometric) to in situ generated *N*-acyl iminium ions in the presence of an achiral ligand (TMPDA) to activate the zinc reagent.[42]



Scheme 1.6. Preparation of functionalized propargylic alcohols and amines by $Zn(OTf)_2$ promoted alkynylation

Early studies by Oppolzer and Radinov of the asymmetric addition of divinylzinc to aldehydes[43] in the presence of chiral amino alcohols have led to the implementation of numerous protocols for the stereoselective synthesis of allylic alcohols.[44] In 1991, Srebnik reported the

F. *Tetrahedron* **1996**, *52*, 7235. (d) Sato, Y.; Nishimata, T.; Mori, M. *Heterocycles* **1997**, *44*, 443. (e) Cossy, J.; Poitevin, C.; Pardo, D. G.; Peglion, J.-L.; Dessinges, A. *Synlett* **1998**, 251. (f) Li, C.-J.; Wei, C. *Chem. Commun.* **2002**, 268. (g) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 2535.

[40] (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. (c) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605.

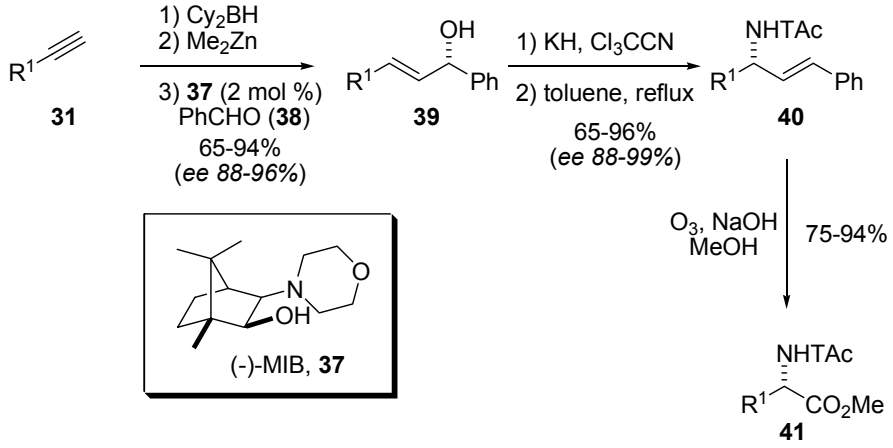
[41] (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245. (b) Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 4319. (c) Fischer, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1497.

[42] For the addition of zinc alkynylides to nitrones, see Fässler, R.; Frantz, D. E.; Oetiker, J.; Carreira, E. M. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 3054.

[43] Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1988**, *29*, 5645.

[44] For a functionally related Ni catalyzed approach to allylic alcohols and amines, see (a) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221. (b) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 1364. (c) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442. (d) Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076. (e) Miller, K. M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 4130. (f) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 3941.

preparation of vinylzinc reagents via transmetalation of alkenylboranes with dialkylzincs, while also studying the migratory properties of alkyl and alkenyl ligands on zinc.[45] Shortly thereafter, Oppolzer and Radinov reported the enantioselective vinylation of aldehydes with vinylzinc halides[46] in the presence of a chiral amino alcohol. They have since modified this approach to incorporate the in situ generation of vinylzinc reagents via the hydroboration-transmetalation pathway of Srebnik in both the inter-[47] and intramolecular[48] variant of this reaction. Recently, Walsh and co-workers adapted this protocol to the enantioselective synthesis of amino acids and allylic amines (Scheme 1.7).[49] The allylic alcohols **39** were prepared by hydroboration of terminal alkynes **31** with dicyclohexylborane followed by transmetalation to zinc and asymmetric addition to benzaldehyde in the presence of Nugent's ligand, MIB.[50] Transposition of the olefin using Overman's trichloracetimidate rearrangement[51] afforded the valuable allylic amides in good to excellent yields with complete transfer of configuration. Oxidative cleavage of the olefin to the methyl ester using Marshall's protocol (O_3, NaOH, MeOH)[52] affords the protected amino acid derivatives **41** in good overall yield.



Scheme 1.7. B→Zn transmetalation and addition to aldehydes: Enantioselective synthesis of amino acids and allylic amines

[45] (a) Srebnik, M. *Tetrahedron Lett.* **1991**, *32*, 2449. (b) Laloe, E.; Srebnik, M. *Tetrahedron Lett.* **1994**, *35*, 5587.
[46] Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1991**, *32*, 5777.
[47] Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*, 170.
[48] (a) Oppolzer, W.; Radinov, R. N.; De Brabander, J. *Tetrahedron Lett.* **1995**, *36*, 2607. (b) Oppolzer, W.; Radinov, R. N.; El-Sayed, E. *J. Org. Chem.* **2001**, *66*, 4766.
[49] Chen, Y. K.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 12225.
[50] Nugent, W. A. *J. Chem. Soc., Chem. Commun.* **1999**, 1369.
[51] (a) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901. (b) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218.
[52] (a) Marshall, J. A.; Garofalo, A. W.; Sedrani, R. C. *Synlett* **1992**, 643. (b) Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675.

Wipf and Xu reported in 1994 that the vinylzinc reagents prepared via the hydrozirconation of alkynes **1** and transmetalation to dimethylzinc underwent smooth addition to aldehydes affording racemic **42** (Table 1.1).[53] Interestingly, whereas alkyl- or alkenylzinc reagents require activation to promote their addition to aldehydes,[54] the addition of alkenylzinc reagents prepared using this protocol proceeds without the requirement of ligand activation. Indeed, it was found that the addition of diethylzinc to aldehydes proceeds in the presence of catalytic amounts of Cp_2ZrCl_2 (conversion ca. 50% in 4 h compared to <5% in the absence of zirconocene catalyst).[55] Accordingly, the presumed byproduct of the Zr→Zn transmetalation ($Cp_2ZrMeCl$) is thought to be responsible for the in situ activation of aldehydes. Subsequently, Wipf and Ribe have extended this protocol to include the asymmetric addition of alkenylzirconocenes to aldehydes in the presence of dimethylzinc and chiral ligands (Table 1.1).[55] Wipf and Xu originally reported that the Zr→Zn reaction proceeded with 38% ee in the presence of the diphenylprolinol ligand **43** (entry 1);[53] however, an induction period was later discovered, and stirring **43** with the vinylzinc reagent for 1 h[56] afforded **42** in 81% ee (entry 1). A switch to van Koten's aminothiol ligand **44** (entry 2, R^4 = Me)[57] resulted in improved enantioselection. Increasing the steric bulk of the aminothiol (entry 3, **45**; R^4 = Et) resulted in a modest improvement in the enantioselectivity. The reaction works well with most aromatic aldehydes (entries 4-8); however, *p*-anisaldehyde afforded **42** with only 63% ee. 3-Hexyne afforded the highest ee for the vinylation of benzaldehyde (entry 9, 99% ee) while aliphatic aldehydes did not perform particularly well under the reaction conditions (entries 10, 11). A strong positive non-linear effect[32] was observed for aminothiol ligand **44**, indicating the likely presence of a dimeric species in solution.[58]

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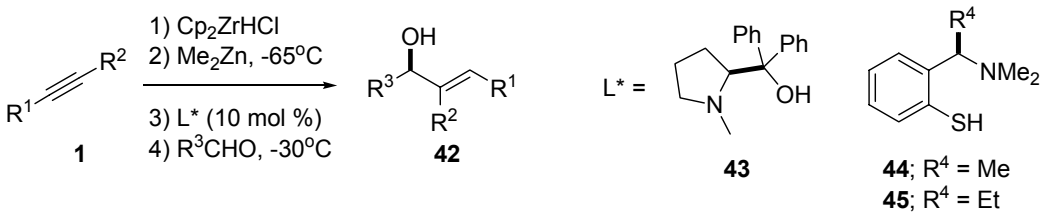
[53] (a) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197. (b) Wipf, P.; Xu, W. *Org. Synth.* **1996**, *74*, 205.
[54] (a) Oguni, N.; Omi, T.; Yamamoto, Y.; Nakamura, A. *Chem. Lett.* **1983**, 841. (b) Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823. (c) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071.
[55] (a) Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454. (b) Ribe, S. D. Ph.D Dissertation, University of Pittsburgh, 2003.
[56] This induction period is believed to be required to maximize the solubility of the ligand metal complex. See ref. 55b for details.
[57] Knotter, D. M.; van Maanen, H. L.; Grove, D. M.; Spek, A. L.; van Koten, G. *Inorg. Chem.* **1991**, *30*, 3309.
[58] Wipf, P.; Jayasuriya, N.; Ribe, S. *Chirality* **2003**, *15*, 208.

Table 1.1. Catalytic asymmetric alkenylzinc addition to aldehydes using the Zr→Zn methodology



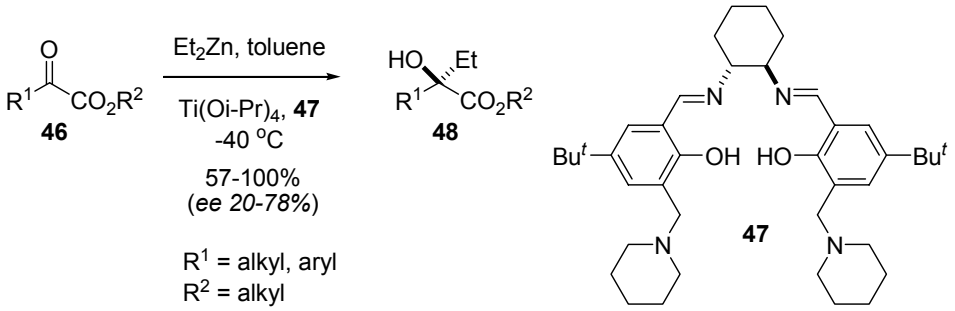
entry	R^1	R^2	R^3	ligand	yield (%)	ee (%)
1	C_4H_9	H	Ph	**43**	92	38 (81[a])
2	C_4H_9	H	Ph	**44**	76	89
3	C_4H_9	H	Ph	**45**	80	95
4	C_4H_9	H	*p*-ClC_6H_4	**45**	83	97
5	C_4H_9	H	*p*-$CF_3C_6H_4$	**45**	71	93
6	C_4H_9	H	*p*-$MeOC_6H_4$	**45**	75	63
7	C_4H_9	H	*m*-$MeOC_6H_4$	**45**	79	99
8	$C(CH_3)_3$	H	Ph	**45**	73	83
9	C_2H_5	C_2H_5	Ph	**45**	66	99
10	C_4H_9	H	*c*-C_6H_{11}	**45**	63	74
11	C_4H_9	H	$PhCH_2CH_2$	**45**	71	64

[a]15 mol % ligand with 1 h induction period

While there are abundant reports on the asymmetric alkylation of aldehydes, the challenge of performing a stereocontrolled addition to ketones has only recently been successfully addressed.[59] There are two major difficulties in this reaction. First, ketones are inherently less reactive than aldehydes as there are two electron-donating alkyl groups. Second, enantiofacial discrimination is challenging since the difference in size between the two substituents is much less apparent with two alkyl groups compared to one alkyl and one hydrogen substituent. α-Keto esters have been used successfully in alkylation reactions and their reactivity is often comparable to aldehydes, and facial discrimination can be accomplished by taking advantage of the chelating properties of the keto ester.[60,61,62] DiMauro and Kozlowski

[59] (a) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445. (b) Ramon, D. J.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1239. (c) Ramon, D. J.; Yus, M. *Tetrahedron* **1998**, *54*, 5651. (d) Garcia, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970. (e) Li, H.; Garcia, C.; Walsh, P. J. *Proc. Nat. Acad. Sci.* **2004**, *101*, 5425.
[60] Kovacs, L. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 471.

have recently accomplished the first catalytic asymmetric ethylation of α-keto esters with diethylzinc (Scheme 1.8).[63] In the absence of catalyst, very little conversion of keto ester **46** to α-hydroxy ester **48** is observed; consequently the allylic alcohol resulting from reduction of the ketone was the major product. After some optimization of the ligand, the titanium complex of **47** was found to afford the ethylated α-hydroxy ester products in good yields with modest enantioselectivities.

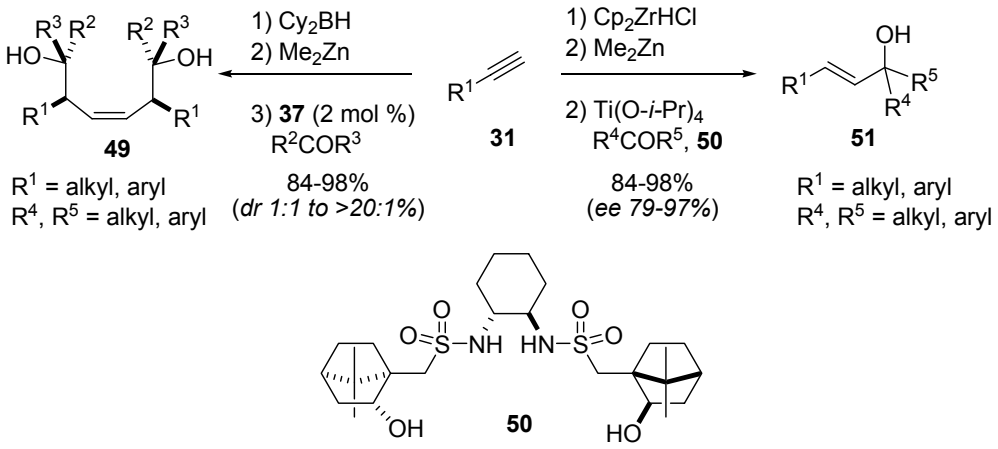


Scheme 1.8. Catalytic asymmetric addition of diethyl zinc to α-keto esters

As part of their continuing work on the asymmetric alkylation of carbonyl compounds with in situ derived zinc reagents, Walsh and co-workers have developed protocols for the asymmetric addition of vinylzinc reagents to ketones (Scheme 1.9).[64] During their initial attempts to extend their methodology for the preparation of allylic alcohols to include the addition to ketones, they observed the formation of an unexpected product.[64a] After careful examination and optimization, the symmetric diol **49** was isolated as the major product, generally with excellent control of diastereoselectivity. Combination of the methodology developed by Wipf and co-workers[55] with the Walsh protocol for the asymmetric alkylation of ketones[59d,e] led to the discovery of an asymmetric vinylation of ketones in the presence of the titanium complex of ligand **50**. To achieve a high degree of facial selectivity, one of the groups

[61] Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953.
[62] (a) Ito, Y.; Sawamura, M.; Hamashima, H.; Emura, T.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 4681. (b) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. J. Am. Chem. Soc. **1999**, *121*, 686. (c) Juhl, K.; Gathergood, N.; Jorgensen, K. A. *J. Chem. Soc., Chem. Commun.* **2000**, 2211. (d) Evans, D. A.; Janey, J. M. *Org. Lett.* **2001**, *3*, 2125. (e) Ghosh, A. K.; Shirai, M. *Tetrahedron Lett.* **2001**, *42*, 6231. (f) Jensen, K. B.; Thorbauge, J.; Hazell, R. G.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160.
[63] (a) DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2002**, *4*, 3781. (b) DiMauro, E. F.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2002**, *124*, 12668.
[64] (a) Garcia, C.; Libra, E. R.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 3210. (b) Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 6538.

of the ketone must be aromatic; however, good enantioselectivity (79%) was observed for the sole example (acyclic) of a dialkyl ketone (R^4 = Me, R^5 = *i*-Bu).



Scheme 1.9. Hydrometalation-transmetalation to zinc and addition to ketones

The first extension of the Wipf methodology to the vinylation of ketones was disclosed in 2001 by Chavez and Jacobsen as part of their total synthesis of the phosphatase inhibitor fostriecin (Scheme 1.10).[65] Hydrozirconation of 1-octyne and transmetalation to zinc followed by reaction with the epoxy ketone **53** afforded the allylic alcohol **54** with excellent control of diasteroselectivity (>30:1). The use of the functionalized alkyne **55** which was required for the synthesis resulted in a lower isolated yield of the desired tertiary allylic alcohol; however the diastereoselectivity was once again excellent and **56** could be elaborated in 9 subsequent steps to the natural product.

The Zr→Zn methodology has been successfully applied by a number of research groups for their efforts toward the total synthesis of various natural products (Figure 1.1). Along with the application towards the preparation of fostriecin, the hydrozirconation-transmetalation to zinc and addition to aldehydes has been used for the preparation of curacin A,[18d] nisamycin,[66] halichlorine,[67] ratjadone,[68] leucascandrolide A,[69] lobatamide C,[70] and laulimalide.[71]

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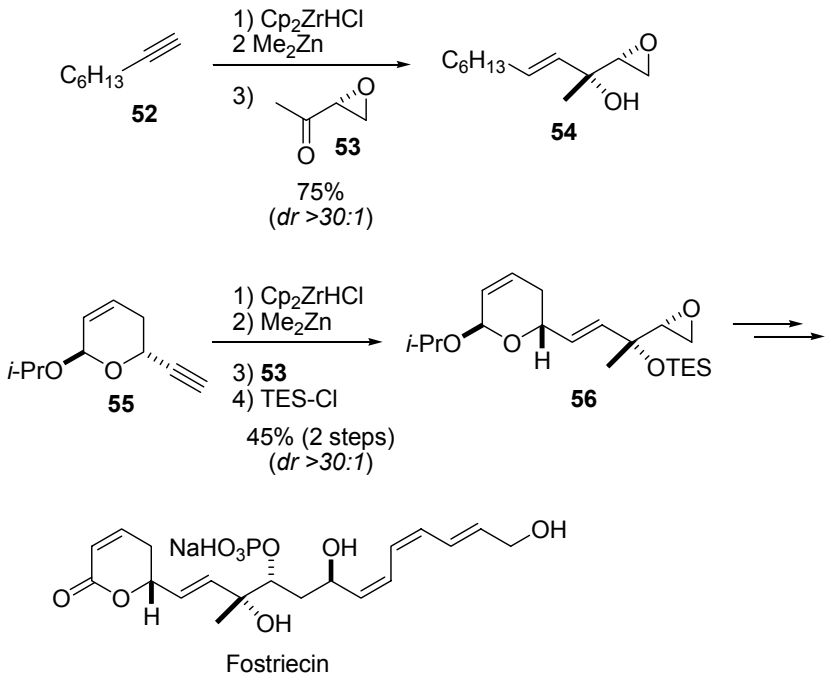
[65] Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 3667.
[66] (a) Wipf, P.; Coish, P. D. G. *Tetrahedron Lett.* **1997**, *38*, 5073. (b) Wipf, P.; Coish, P. D. G. *J. Org. Chem.* **1999**, *64*, 5053.
[67] Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3542.
[68] Williams, D. R.; Ihle, D. C.; Plummer, S. V. *Org. Lett.* **2001**, *3*, 1383.
[69] (a) Wipf, P.; Reeves, J. T. *Chem. Commun.* **2002**, 2066. (b) Williams, D. R.; Plummer, S. V.; Patnaik, S. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 3934.



Scheme 1.10. Zr→Zn transmetalation and addition to an α,β-epoxyketone: Jacobsen's total synthesis of fostriecin

[70] (a) Shen, R.; Lin, C. T.; Porco Jr., J. A. *J. Am. Chem. Soc.* **2002**, *124*, 5650. (b) Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco Jr., J. A. *J. Am. Chem. Soc.* **2003**, *125*, 7889.
[71] Williams, D. R.; Mi, L.; Mullins, R. J.; Stites, R. E. *Tetrahedron Lett.* **2002**, *43*, 4841.

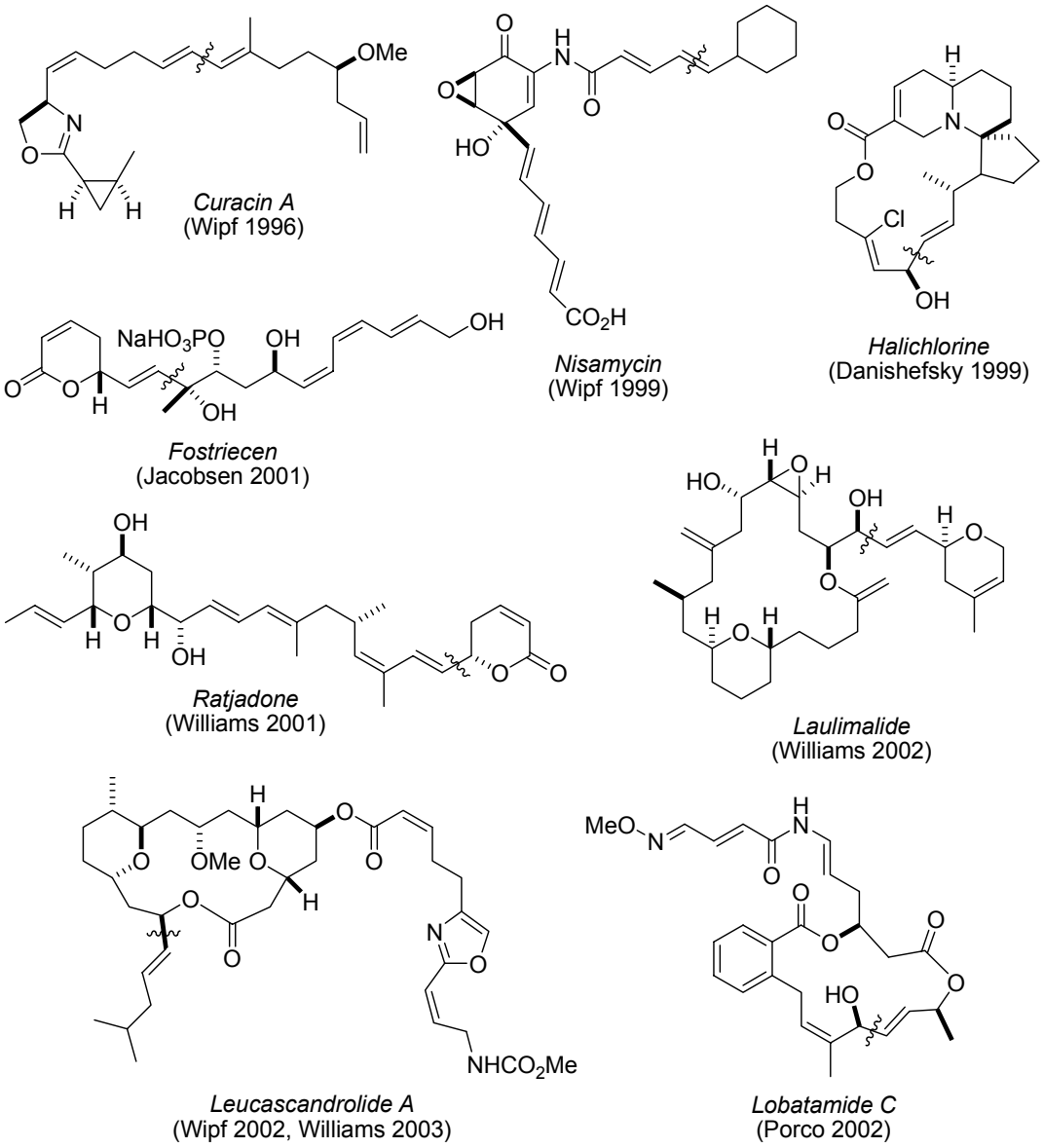


Figure 1.1. Applications of the Zr→Zn methodology in total synthesis[72]

[72] The bond formed using the Zr→Zn methodology is labeled in the figure.

1.1.3 Simmons-Smith Cyclopropanation Reactions

Our studies toward the preparation of allylic amines using the Zr→Zn methodology have led to the discovery of a novel reaction pathway which affords *C*-cyclopropylalkylamides in good yields and with excellent diastereofacial control. This reaction presumably occurs via the directed Simmons-Smith cyclopropanation of the intermediate allylic amide.[73,74] Nearly thirty years after the original report of the preparation of $IZnCH_2I$ by Emschwiller,[75] Simmons and Smith reported that this reagent was useful for the stereospecific synthesis of cyclopropanes from alkenes,[73] and it has become known as the Simmons-Smith reagent. While a number of metals other than zinc have been shown to be effective for the cyclopropanation of olefins,[76,77,78] zinc reagents are the most broadly utilized. Of the most prominently used metals, samarium and zinc exhibit excellent chemoselectivity for allylic alcohols in the presence of other alkenes while aluminum reagents will react with isolated olefins in the presence of allylic alcohols (Table 1.2).[79] The cyclopropanation of geraniol proceeds with excellent control of regioselectivity for the allylic alcohol when zinc and samarium reagents are used (entries 1, 3). Conversely, the aluminum based reagent affords almost exclusively cyclopropane at the distal olefin site (entry 2). There have been reports that initial deprotonation of allylic alcohols facilitates the directed cyclopropanation reaction, however in this case there appears to be little effect on the regioselectivity (entries 4-7).[80] The Shi reagent, the most reactive cyclopropanating reagent prepared to date ($CF_3CO_2ZnCH_2I$), affords a statistical mixture of products (entry 8).[81] If the

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[73] (a) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323. (b) Smith, H. E.; Simmons, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256.

[74] (a) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React.* **1973**, *20*, 1. (b) Charette, A. B.; Beauchemin, A. *Org. React.* **2001**, *58*, 1. (c) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.

[75] Emschwiller, G. C. R. *Hebd. Seance Acad. Sci.* **1929**, *188*, 1555.

[76] For the cyclopropanation of alkenes with metal carbenoids ($M\text{-}CH_2X$) from metals other than Al, Sm and Zn, see (a) Hoberg, H. *Liebigs Ann. Chem.* **1962**, *656*, 1. (b) Miller, D. B. *Tetrahedron Lett.* **1964**, *5*, 989. (c) Seyferth, D.; Eisert, M. A.; Todd, L. J. *J. Am. Chem. Soc.* **1964**, *86*, 121. (d) Furukawa, J.; Kawabata, N.; Fujita, T. *Tetrahedron* **1970**, *26*, 243. (e) Seyferth, D.; Andrews, S. B. *J. Organomet. Chem.* **1971**, *30*, 151. (f) Kawabata, N.; Naka, M.; Yamashita, S. *J. Am. Chem. Soc.* **1976**, *98*, 2676. (f) Maruoka, K.; Fukutani, Y.; Yamamoto, H. *J. Org. Chem.* **1985**, *50*, 4412.

[77] For a recent review on the cyclopropanation of alkenes using transition metal stabilized carbenes ($M{=}CH_2$), prepared by transition metal-mediated decomposition of diazo compounds, see Davies, H. L. M.; Antoulinakis, E. G. *Org. React.* **2001**, *57*, 1.

[78] Corey, E. J.; Chaykovsky, M. J. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

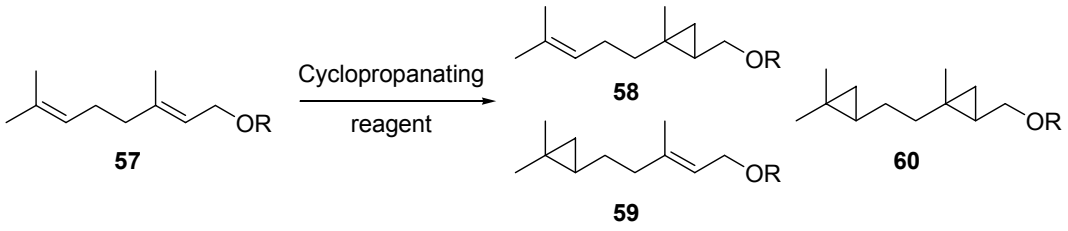
[79] Charette, A. B.; Beauchemin, A. *J. Organomet. Chem.* **2001**, *617-618*, 702.

[80] These protocols do, however, reduce the amount of CH_2I_2 required in the reaction.

[81] This reagent was introduced by Shi and co-workers and is reported to be the best reagent for the cyclopropanation of unactivated olefins. It has also been reported as an efficient reagent for the *anti*-cyclopropanation of acyclic

corresponding benzyl ether of **57** is reacted under any of these conditions, cyclopropanation is favored at the olefin proximal to the ether functionality (entries 9-14).

Table 1.2. Chemoselectivity of metal carbenoid cyclopropanation of geraniol derivatives



entry	R	deprotonation	carbenoid	**58**:**59**:**60**
1	H	none	Et_2Zn, CH_2I_2	74:2:3
2	H	none	*i*-Bu_3Al, CH_2I_2	1:76:4
3	H	none	Sm(Hg), ICH_2Cl	98:0:0
4	H	Et_2Zn	$EtZnCH_2I$	80:2:8
5	H	Et_2Zn	$Zn(CH_2I)_2$	88:2:6
6	H	Et_2Zn	$Zn(CH_2I)_2$•DME	70:2:1
7	H	Et_2Zn	$IZnCH_2I$•Et_2O	91:2:3
8	H	Et_2Zn	$CF_3CO_2ZnCH_2I$	31:32:19
9	Bn	n/a	*i*-Bu_3Al, CH_2I_2	67:0:0
10	Bn	n/a	Sm(Hg), ICH_2Cl	75:0:0
11	Bn	n/a	$EtZnCH_2I$	92:0:1
12	Bn	n/a	$Zn(CH_2I)_2$	97:0:1
13	Bn	n/a	$IZnCH_2I$•Et_2O	92:0:0
14	Bn	n/a	$CF_3CO_2ZnCH_2I$	91:0:6

The three foremost methods for the preparation of zinc-based cyclopropanating reagents are oxidative addition,[73] alkyl exchange[82] and nucleophilic displacement (Figure 1.2).[83] Oxidative addition (activated Zn metal and CH_2X_2) is the oldest and most common method for the generation of the Simmons-Smith reagent for cyclopropanations involving zinc. While this is

allylic ethers (ref. 81b). See (a) Yang, Z.; Lorenz, J. C.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 8621. (b) Charette, A. B.; Lacasse, M.-C. *Org. Lett.* **2002**, *4*, 3351. (c) Lorenz, J. C.; Long, J.; Yang, Z.; Xue, S.; Xie, Y.; Shi, Y. *J. Org. Chem.* **2004**, *69*, 327.

[82] (a) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, *7*, 3353. (b) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53.

[83] (a) Wittig, G.; Schwarzenback, K. *Angew. Chem.* **1959**, *71*, 652. (b) Wittig, G.; Wingler, F. *Chem. Ber.* **1964**, *97*, 2146.

the most stable form of the reagent, it is also the least reactive, since the electrophilic character of the reagent is retarded due to the necessary use of an ether solvent (THF, Et_2O, DME).[84] The alkyl exchange reaction[82,85] is now the method of choice for generating reactive zinc-derived cyclopropanating reagents affording the highest degree of diastereoselectivity[86] in directed Simmons-Smith reactions.[87] It has been noted that this exchange process is accelerated by traces of oxygen in the solvent,[88] and the adventitious oxygen in the solvent is usually sufficient to catalyze this process. The major advantage of this protocol is that the reactions proceed in non-coordinating solvents (CH_2Cl_2, $Cl(CH_2)_2Cl$), and both reagents (Et_2Zn and CH_2X_2) are commercially available and can be used without purification. The reactivity of these reagents is greater than those prepared by oxidative addition; however, their stability is significantly lower.[87] Finally, treatment of ZnI_2 with diazomethane to form $IZnCH_2I$ or $Zn(CH_2I)_2$ was reported by Wittig in 1959, but this procedure is now rarely employed for cyclopropanation reactions.[83]

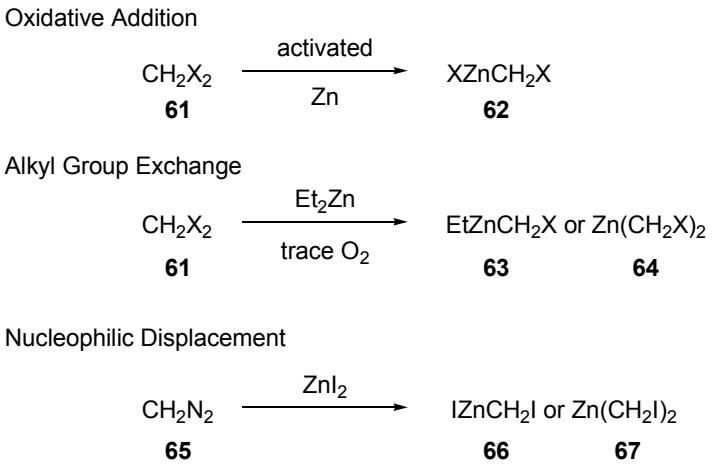


Figure 1.2. Preparation of zinc carbenoids

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[84] Charette, A. B.; Marcoux, J.-F. *Synlett* **1995**, 1197.

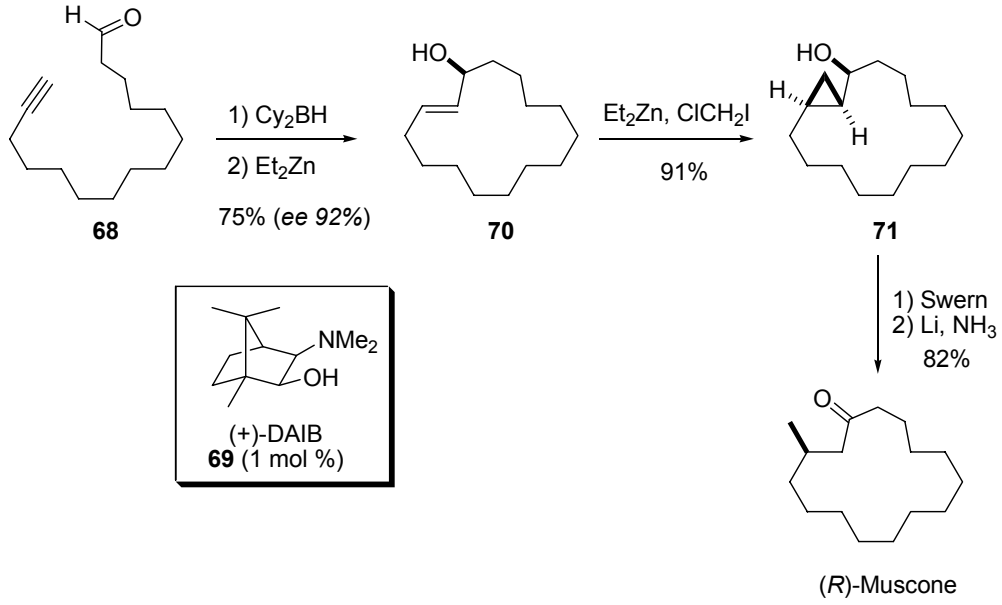
[85] $EtZnCH_2I$ is commonly referred to as Furukawa's reagent. While the diastereoselectivities observed using this reagent are often best, the reagent stability is poor as it readily decomposes to PrZnI. In these cases, excess CH_2I_2 is usually employed, generating $IZnCH_2I$ (Simmons-Smith reagent) from the decomposition product, PrZnI.

[86] Charette, A. B.; Lebel, H. *J. Org. Chem.* **1995**, *60*, 2966.

[87] For structural characterization and commentary on the stability of various zinc carbenoids, see (a) Denmark, S. E.; Edwards, J. P.; Wilson, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 723. (b) Denmark, S. E.; Edwards, J. P.; Wilson, S. R. *J. Am. Chem. Soc.* **1992**, *114*, 2592. (c) Charette, A. B.; Brochu, C. *J. Am. Chem. Soc.* **1995**, *117*, 11367. (d) Charette, A. B.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1996**, *118*, 4539. (e) Charette, A. B.; Marcoux, J.-F.; Bélanger-Gariépy, F. *J. Am. Chem. Soc.* **1996**, *118*, 6792. (f) Charette, A. B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* **2001**, *123*, 12160. (f) Charette, A.; Beauchemin, A.; Francoeur, S.; Bélanger-Gariépy, F.; Enright, G. D. *Chem. Commun.* **2002**, 466.

[88] (a) Miyano, S.; Hashimoto, H. *J. Chem. Soc., Chem. Commun.* **1971**, 1418. (b) Miyano, S.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 892.

The Simmons-Smith cyclopropanation reaction is greatly influenced by adjacent Lewis basic functionality (ie, alcohols, ethers, amides, etc.). The hydroxyl-directed Simmons-Smith cyclopropanation reaction was beautifully employed by Oppolzer and co-workers in the synthesis of (*R*)-muscone, highlighting their methodology for the asymmetric formation of allylic alcohols (Scheme 1.11).[89] Hydroboration of ω-ynal **68** followed by transmetalation to zinc and intramolecular vinylation of the aldehyde in the presence of Noyori's DAIB ligand[90] afforded allylic alcohol **70** (75%, 92% ee). The allylic alcohol was subjected to Denmark's cyclopropanation conditions[91] affording the desired *syn*-cyclopropylcarbinol **71** as a single diastereomer.[92] Oxidation to the known ketone[93] followed by reductive opening of the cyclopropane (Li, NH_3) afforded (*R*)-muscone.



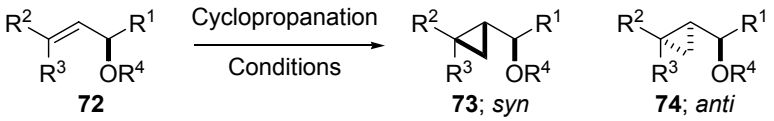
Scheme 1.11. Oppolzer's synthesis of muscone: Hydroxy-directed cyclopropanation of a cyclic olefin

For acyclic systems, the cyclopropanation of chiral allylic alcohols will generally favor the *syn*-diastereomer whereas chiral allylic ethers tend to favor the *anti*-diastereomer (Table 1.3).

[89] Oppolzer, W.; Radinov, R. N. *J. Am. Chem. Soc.* **1993**, *115*, 1593.
[90] Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M. *Pure Appl. Chem.* **1988**, *60*, 1597.
[91] Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974.
[92] For a review on substrate directed reactions, see Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
[93] Nelson, K. A.; Mash, E. A. *J. Org. Chem.* **1986**, *51*, 2721.

The traditional Simmons-Smith reagent affords a nearly 1:1 mixture of *syn*- and *anti*-alcohols **73** and **74** (entry 1). Using the Furukawa reagent, this ratio is greatly improved (entry 2) and as the size of R^1 increases, the selectivity for the *syn*-product increases, while R^2 seems to have little effect on the selectivity (data not shown). Alkyl ethers favor the *anti*-diastereomer **74**, however, as the steric bulk of R^1 increases, the selectivity switches to favor the *syn*-isomer **73**. For compounds where $R^3 \neq H$, the *syn*-diastereomer is always favored for both alcohols and ethers, however the choice of reagent is paramount to achieve optimal selectivity. The exception is when the Shi reagent is used for the cyclopropanation of silyl protected allylic alcohols; very good *anti*-selectivity has been observed regardless of the substitution pattern at the olefin.

Table 1.3. Simmons-Smith cyclopropanation of acyclic allylic alcohols and ethers



72 **73**; *syn* **74**; *anti*

entry	R^1	R^2	R^3	R^4	carbenoid	**73**:**74**
1	Me	Me	H	H	Zn/Cu, CH_2I_2	56:44
2	Me	Me	H	H	Et_2Zn, CH_2I_2	86:14
3	Ph	Me	H	H	Et_2Zn, CH_2I_2	>98:2
4	*i*-Pr	Ph	H	H	Et_2Zn, CH_2I_2	>98:2
5	Me	Ph	H	Bn	Et_2Zn, CH_2I_2	10:90
6	Et	Ph	H	Bn	Et_2Zn, CH_2I_2	33:67
7	*i*-Pr	Ph	H	Bn	Et_2Zn, CH_2I_2	95:5
8	Me	Ph	H	TBS	$CF_3CO_2ZnCH_2I$	2:98
9	Me	H	$Ph(CH_2)_3$	Bn	Et_2Zn, CH_2I_2	15:1
10	Me	H	$Ph(CH_2)_2$	TIPS	$CF_3CO_2ZnCH_2I$	3:97

Two limiting transition states for the cyclopropanation of allylic ethers (R = PG) and alcohols (R = ZnX; A and B, Figure 1.3) have been proposed by Charette to explain the outcome of the directed cyclopropanation reactions.[78b,94,95] A bridging metal (L_nMX) has been proposed to account for the observed acceleration of Simmons-Smith cyclopropanation in the presence of

[94] Charette, A. B.; Lebel, H.; Gagnon, A. *Tetrahedron* **1999**, *55*, 8845.
[95] For recent transition state calculations of the Simmons-Smith cyclopropanation reaction, see (a) Bernardi, F.; Bottoni, A.; Miscione, G. P. *J. Am. Chem. Soc.* **1997**, *119*, 12300. (b) Nakamura, E.; Hirai, A.; Nakamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5844. (c) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 2341.

Lewis acids.[96,97] For allylic alcohols, the transition state in which $A^{1,3}$-strain is minimized predominates (particularly when $R^1 \neq H$), affording the *syn*-diastereomer via transition state B. This model also minimizes the interaction of the incoming carbenoid with R^4. The driving force for *anti*-selectivity in the case of allylic ethers is the unfavorable gauche interaction between the protective group R and R^4. However, as the steric bulk of R^4 increases, the minimization of allylic strain once again predominates and the *syn*-diastereomer is favored (Table 1.3, entries 5-7).

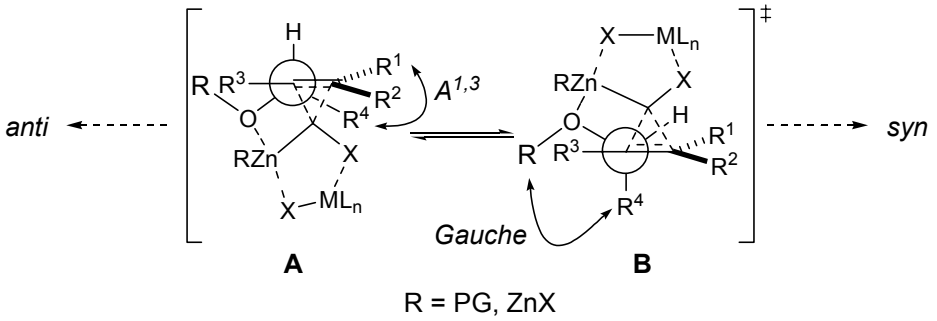
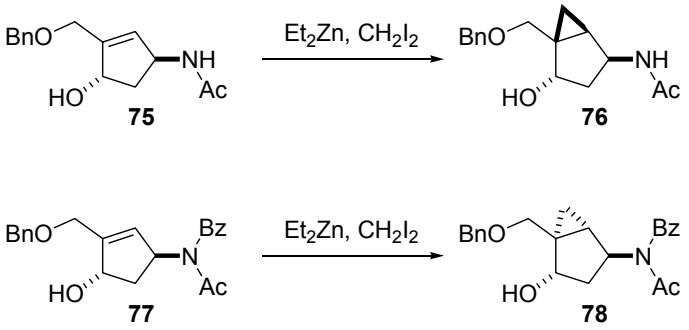


Figure 1.3. Transition states for the directed cyclopropanation of chiral allylic alcohols and ethers

While there are numerous examples of oxygen-directed cyclopropanation reactions, there are only a few examples of nitrogen-directed Simmons-Smith cyclopropanation reactions of allylic amines (vide infra) or amides.[98] However, an interesting study by Marquez and co-workers compared the diastereofacial directing power of an amide to a hydroxy group in the cyclopropanation of a cyclopentene derivative (Scheme 1.12).[98c] The unprotected amide **75** directs the cyclopropanation *syn* to the amide functionality (*anti* to the hydroxy group). Conversely, when the amide is doubly protected with an acetate and benzoate as in **77**, the hydroxy group directs the cyclopropanation *syn* to the hydroxyl (*anti* to the amide). On the basis of these results, a secondary amide is a stronger directing group than a hydroxyl functionality.

[96] For a review on the bonding in bridged transition metal complexes, see Holton, J.; Lappert, M. F.; Pearce, R.; Yarrow, P. I. W. *Chem. Rev.* **1983**, *83*, 135.
[97] (a) Wittig, G.; Wingler, F. *Chem. Ber.* **1964**, *97*, 2146. (b) Friedrich, E. C.; Lunetta, S. E.; Lewis, E. J. *J. Org. Chem.* **1989**, *54*, 2388. (c) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651. (d) Denmark, S. E.; O' Connor, S. P. *J. Org. Chem.* **1997**, *62*, 3390.
[98] (a) Avramoff, M. *Eur. J. Med. Chem.* **1981**, *16*, 199. (b) Russ, P.; Ezzitouni, A.; Marquez, V. E. *Tetrahedron Lett.* **1997**, *38*, 723. (c) Russ, P.; Ezzitouni, A.; Marquez, V. E. *J. Org. Chem.* **1997**, *62*, 4870. (d) Aggarwal, V. K.; Fang, G. Y.; Meek, G. *Org. Lett.* **2003**, *5*, 4417.

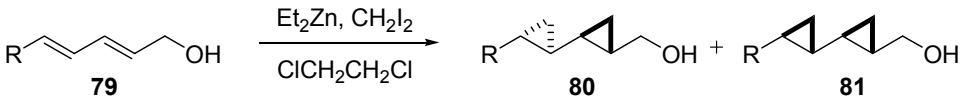
Unfortunately, there have not been any studies reported for this competition in an acyclic system such that the conformational bias of the ring could be completely discounted.



Scheme 1.12. Hydroxy vs. amide in the directed Simmons-Smith cyclopropanation

As part of their studies directed towards the synthesis of the oligocyclopropane-containing natural product FR-900848,[99,100] Barrett and Tustin described their findings of the diastereoselective cyclopropanation of dienyl alcohols **79** (Table 1.4).[101] The *anti*-diastereomer **80** was favored in all cases, although the selectivity increases with the size of R. Barrett rationalized the observed selectivity by using a combination of stereoelectronic and steric effects; however, $A^{1,3}$-strain arguments alone can also be used to correctly predict the stereochemical outcome of this reaction.

Table 1.4. Simmons-Smith cyclopropanation of dienylalcohols: Synthesis of bicyclopropanes



entry	R	yield (%)	diastereomeric ratio **80**:**81**
1	Me	68	5:1
2	Ph	80	5:1
3	*i*-Pr	72	6:1
4	C_6H_{11}	78	7:1
5	$TBDPSOCH_2$	72	>95:5

[99] For a review on oligocyclopropyl-containing natural products, see Pietruszka, J. *Chem. Rev.* **2003**, *103*, 1051.
[100] For Barrett's total synthesis of FR-900848, see (a) Barrett, A. G. M.; Kasdorf, K. *J. Chem. Soc., Chem. Commun.* **1996**, 325. (b) Barrett, A. G. M.; Doubleday, W. W.; Kasdorf, K.; Tustin, G. J. *J. Org. Chem.* **1996**, *61*, 3280.
[101] Barrett, A. G. M.; Tustin, G. J. *J. Chem. Soc., Chem. Commun.* **1995**, 355.

Methylenecyclopropanes are valuable intermediates in organic synthesis having found use in the Ni(0)- or Pd(0)-catalyzed reaction with alkenes and alkynes for the formation of 5-membered rings.[102,103] Lautens and Delanghe have recently applied the Simmons-Smith cyclopropanation reaction of allenyl alcohols for the regio- and diastereocontrolled preparation of methylenecyclopropanes (Table 1.5).[104] While the majority of cyclopropanating reagents afforded a poor selectivity for methylenecyclopropanes**83** and **84** over spiropentanes **85** and **86**, excellent selectivities were observed when the allenyl alcohol **82** was pretreated with base prior to introduction of the cyclopropanating reagent (entry 6). Interestingly, similar results were also obtained without the requirement for base treatment using Molander's samarium-mediated cyclopropanation conditions (entry 7).[105]

Charette and co-workers have also investigated the formation of spiropentanes;[106,107] they have successfully extended the application of their asymmetric cyclopropanation reaction[96c,108] of allylic alcohols in the presence of chiral dioxaborolane ligand **88** to the achiral allenyl alcohols **87** (Scheme 1.13). Accordingly, treatment of **87** with the DME complex of $Zn(CH_2I)_2$ (3 equiv) in the presence of **88** (1.2 equiv) afforded the spiropentanes **89** in very good yields and enantioselectivities with the sole exception of the terminally diphenyl-substituted allene.

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[102] For a review on the preparation of heterocycles from alkylidenecyclopropanes, see Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213.

[103] For representative examples, see (a) Noyori, R.; Odagi, T.; Takaya, H. J. Am. Chem. Soc. 1970, 92, 5780. (b) Ohta, T.; Takaya, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 1185. (c) Brandi, A.; Cordero, F.; De Sarlo, F.; Goti, A.; Guarna, A. *Synlett* **1993**, 1. (d) Es-Sayed, M.; Heiner, T.; de Meijere, A. *Synlett* **1993**, 57.

[104] (a) Lautens, M.; Delanghe, P. H. M. *J. Org. Chem.* **1993**, *58*, 5037. (b) Lautens, M.; Delanghe, P. H. M. *J. Am. Chem. Soc.* **1994**, *116*, 8526.

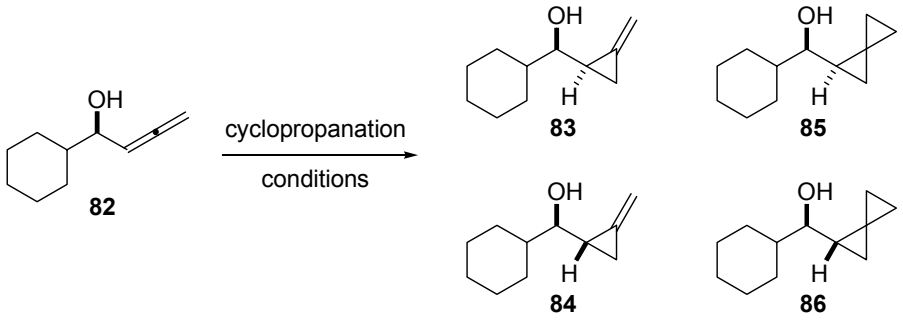
[105] (a) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1987**, *52*, 3942. (b) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1989**, *54*, 3525.

[106] For a review on oligospirocyclopropanes, see de Meijere, A.; Kozhushkov, S. I. *Chem. Rev.* **2000**, *100*, 93.

[107] Charette, A. B.; Jolicoeur, E.; Bydlinski, G. A. S. *Org. Lett.* **2001**, *3*, 3293.

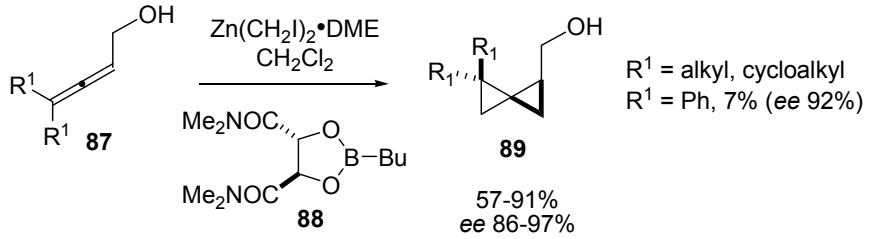
[108] (a) Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081. (b) Charette, A. B.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120*, 11943.

Table 1.5. Simmons-Smith cyclopropanation of allenic alcohols: Chemoselective synthesis of methylenecyclopropanes



entry	metal (equiv)	dihalomethane (equiv)	**83**:**84**:**85**:**86**	conversion
1	Zn(Cu) (2)	CH_2I_2 (2)	83:17[a]	40
2	Zn(Cu) (5)	CH_2I_2 (3.5)	27:54[a]	100
3	Et_2Zn (1)	$ClCH_2I$ (1)	67:3:20:10	69
4	Et_2Zn (2.1)	CH_2I_2 (2.1)	45:55[a]	92
5	Et_3Al (1.2)	CH_2I_2 (1.2)	ND	<5
6	Et_2Zn (1)	$ClCH_2I$ (1)	91:2:4:3[b]	83
7	Sm (10)	$ClCH_2I$ (10)	90:10:0:0	82[c]

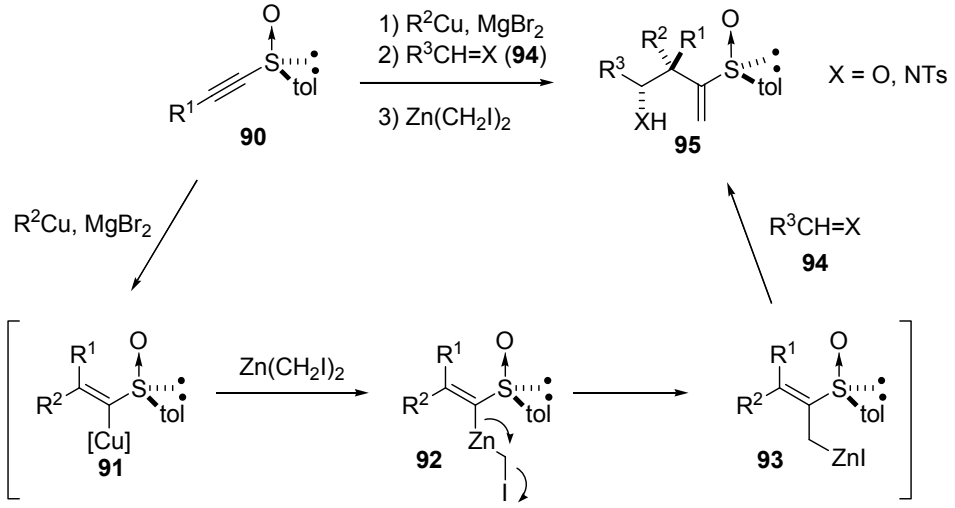
[a]Ratio of (**83**:**84**):(**85**:**86**), **83**:**84** and **85**:**86** not determined; [b]**82** was deprotonated prior to carbenoid addition; [c]Yield of isolated product



Scheme 1.13. Enantioselective formation of spiropentanes via the Simmons-Smith cyclopropanation reaction

The vast majority of applications of Simmons-Smith reagents in synthesis is in the preparation of cyclopropanes; however, the zinc carbenoids have also been found to be useful for

the homologation of organometallic reagents.[109,110] Recently, Marek and co-workers have developed a four-component reaction incorporating the zinc carbenoid mediated homologation of an alkenyl copper species (Scheme 1.14).[111,112] Carbocupration[113] of the chiral alkynyl sulfoxide **90** affords the intermediate vinyl copper species **91** which is treated with $Zn(CH_2I)_2$ to afford the vinylzinc reagent **92**. The intermediate vinylzinc reagent undergoes a rearrangement to afford the reactive allylzinc intermediate which adds to aldehydes or imines with excellent diastereocontrol (*dr* 20-99:1)[114] affording the homoallylic alcohols or amides in good yield (60-88%).

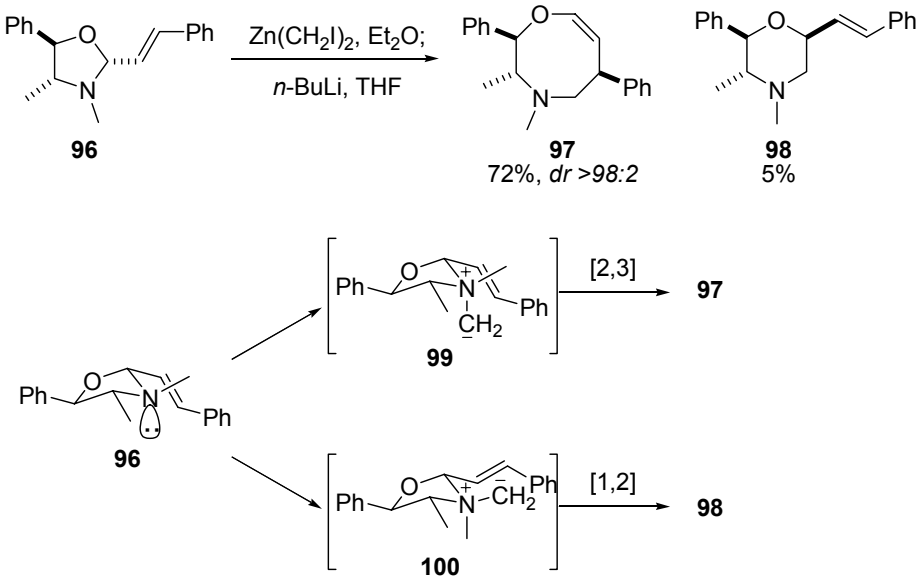


Scheme 1.14. Zinc carbenoid mediated homologation of alkenylcopper reagents: Diastereoselective allylation of aldehydes and imines

Unlike allylic alcohols, allylic amines usually can not be used in the Simmons-Smith cyclopropanation due to ammonium ylide formation.[115] Over 40 years ago, the reaction of the Simmons-Smith reagent with trimethylamine was reported by Wittig and Schwarzenbach to

[109] (a) Knochel, P.; Jeong, N.; Rozema, M. J.; Yeh, M. C. P. *J. Am. Chem. Soc.* **1989**, *111*, 6476. (b) Knochel, P.; Chou, T.-S.; Chen, H. G.; Yeh, M. C. P.; Rozema, M. *J. Org. Chem.* **1989**, *54*, 5202. (c) Knochel, P.; Rao, S. A. *J. Am. Chem. Soc.* **1990**, *112*, 6146. (d) Sidduri, A.; Rozema, M. J.; Knochel, P. *J. Org. Chem.* **1993**, *58*, 2694.
[110] For a recent review on the homologation of sp^3 zinc carbenoids, see Marek, I. *Tetrahedron* **2002**, *58*, 9463.
[111] Sklute, G.; Amsallem, D.; Shabli, A.; Varghese, J. P.; Marek, I. *J. Am. Chem. Soc.* **2003**, *125*, 11776.
[112] Abramovitch, A.; Varghese, J. P.; Marek, I. *Org. Lett.* **2004**, *6*, 621.
[113] (a) Truce, W. E.; Lusch, M. J. J. *J. Org. Chem.* **1974**, *39*, 3174. (b) Truce, W. E.; Lusch, M. J. J. *J. Org. Chem.* **1978**, *43*, 2252. (c) Fiandanese, V.; Marchese, G.; Naso, F. *Tetrahedron Lett.* **1978**, *19*, 5131.
[114] The observed diastereoselectivity when R^1 = H was considerably lower (4:1).
[115] For an example of a Simmons-Smith cyclopropanation reaction using an allylic amine, see ref. 98d.

afford quaternary ammonium salts, presumably via an intermediate ammonium ylide.[116] Recently, Aggarwal and co-workers have taken advantage of this method to initiate the [2,3] sigmatropic rearrangement of allylic amines (Scheme 1.15).[117] During the course of their studies, they found that the ammonium ylides would not undergo the desired rearrangement with the Simmons-Smith reagent alone, however, upon treatment with *n*-BuLi, the zinc ate complex is formed affording the product of [2,3] sigmatropic rearrangement. Accordingly, treatment of **96** with $Zn(CH_2I)_2$ followed by *n*-BuLi affords predominantly oxacine **97** arising from the [2,3] sigmatropic rearrangement with a small amount of the [1,2] product **98**. Alkylation occurs on the same face as the substituent at the 2-positions of the oxazolidine, affording a diastereomeric mixture of ammonium ylides **99** and **100**. [2,3]-Sigmatropic rearrangements have been found experimentally to be faster than the competing [1,2] or Stevens rearrangement, accounting for the formation of **97** from **99**. However, the competing [2,3] rearrangement of **100** would afford an oxacine-containing a highly strained (*E*)- olefin, and only the Stevens product **98** is observed.



Scheme 1.15. Sigmatropic rearrangements of ammonium ylides generated from tertiary amines and Zn carbenoids

[116] Wittig, G.; Schwarzenbach, K. *Liebigs Ann. Chem.* **1961**, *650*, 1.
[117] Aggarwal, V. K.; Fang, G.; Charmant, J. P. H.; Meek, G. *Org. Lett.* **2003**, *5*, 1757.

1.1.4 Reactions of Strained Bicycloalkanes

During the course of our studies on the reactivity of imines with in situ generated alkenylzinc reagents, a cascade process was discovered which involved the intermediacy of a bicyclo[1.1.0]butane.[118] As early as 1905, there were reports on the preparation of bicyclo[1.1.0]butanes, however, these protocols were subsequently found to be irreproducible.[119] The results were also questioned due to the use of highly acidic conditions, and bicyclobutanes are now known to undergo ring-opening at pH < 4. The first verified synthesis of a bicyclobutane was achieved by Wiberg and co-workers in 1959, and there are now numerous reports on their preparation.[118a] These strained bicycloalkanes are interesting intermediates whose physical properties and reactivity patterns have been studied extensively (Figure 1.4). In contrast to bicyclo[2.1.0]pentane, the strain energy of bicyclo[1.1.0]butane (66 kcal/mol) is not the sum of its parts; it is considerably more than twice that observed for cyclopropane (27 kcal/mol) whereas the strain energy of bicyclopentane (51 kcal/mol) is approximately the sum of strain in cyclopropane and cyclobutane (26 kcal/mol) . The puckered nature ($\theta \sim 126$ °) of bicyclobutane differentiates the exo- and endo-hydrogens in the ^{1}H NMR. The exo hydrogens (H_a) for unsymmetrical bicyclobutanes are often observed as an AB quartet, coupled through a W arrangement. Conversely, the endo-hydrogens often appear as singlets. For simple bicyclobutanes, these hydrogens can be interconverted by inversion although the calculated barrier for inversion is large (47 kcal/mol).[120]

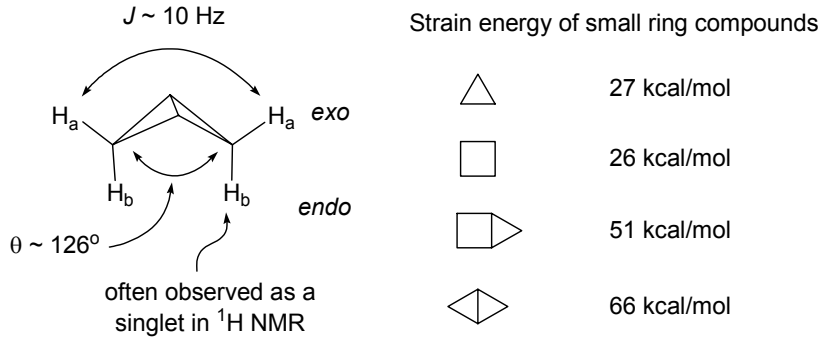


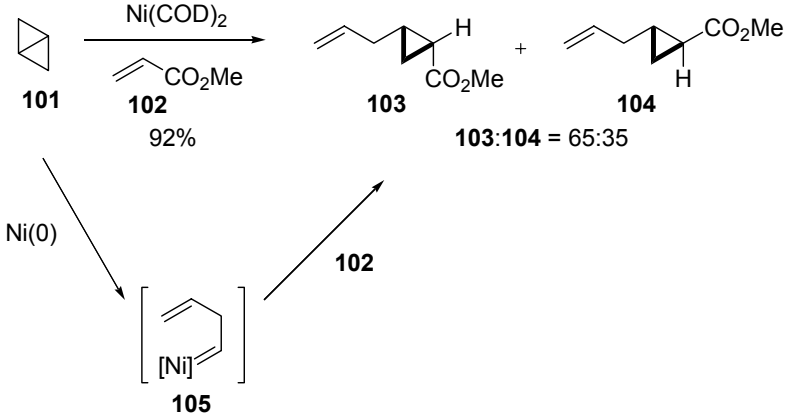
Figure 1.4. Some physical properties of bicyclo[1.1.0]butanes

[118] (a) Wiberg, K. B.; Ciula, R. P. *J. Am. Chem. Soc.* **1959**, *81*, 5261. (b) Wiberg, K. B.; Lampman, G. M. *Tetrahedron Lett.* **1963**, *4*, 2173. (c) Wiberg, K. B.; Lampman, G. M.; Ciula, R. P.; Connor, D. S.; Schertler, P.; Lavanish, J. *Tetrahedron* **1965**, *21*, 2749.

[119] These early studies also did not benefit from modern spectroscopic analytical tools. *Cf.* Perkin, W. H.; Simonsen, J. L. *Proc. Chem. Soc.* **1905**, *21*, 256.

[120] Nguyen, K. A.; Gordon, M. S.; Boatz, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 9241.

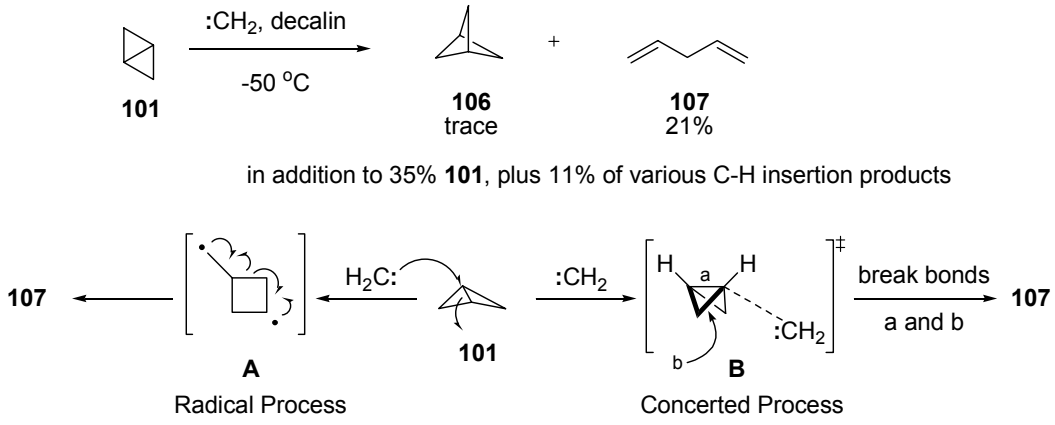
The reactivity of bicyclobutanes revolves primarily around the central bond which has been suggested to have 96% *p* character.[121] Accordingly, many of the reactions of alkenes are also possible for bicyclobutanes and the central bond undergoes polymerization reactions,[122] addition of halogens and alcohols,[118c] and will react with benzyne intermediates[123] and radicals.[124] Perhaps the most intriguing facet of bicyclobutane reactivity is their reaction with transition metals.[125] The majority of these metals afford allyl carbene metal complexes,[126] often followed by a 1,2-hydrogen shift to afford conjugated dienes.[127] Noyori and co-workers have developed the Ni(0)-catalyzed reaction of bicyclobutanes with electron deficient alkenes.[128] For example, reaction of bicyclobutane in methyl acrylate in the presence of 5 mol % $Ni(COD)_2$ afforded a 65:35 mixture of cyclopropanes **103** and **104** in 92% yield via the proposed intermediate allyl carbene nickel complex **105** (Scheme 1.16).



Scheme 1.16. Ni(0) mediated carbene formation from bicyclo[1.1.0]butanes

[121] Newton, M. D.; Schulman, J. M. *J. Am. Chem. Soc.* **1972**, *94*, 767.
[122] (a) Hall Jr., H. K.; Smith, C. D.; Blanchard Jr., E. P.; Cherkofsky, S. C.; Sieja, J. B. *J. Am. Chem. Soc.* **1971**, *93*, 121. (b) Chen, X.-P.; Padias, A. B.; Hall Jr., H. K. *Macromolecules* **2001**, *34*, 3514. (c) Chen, X.-P.; Padias, A. B.; Hall Jr., H. K. *Macromolecules* **2002**, *35*, 3328.
[123] Pomeranz, M.; Wilke, R. N.; Gruber, G. W.; Roy, U. *J. Am. Chem. Soc.* **1972**, *94*, 2752.
[124] Hall, J. K.; Blanchard, E. P.; Cherkofsky, S. C.; Sieja, J. B.; Sheppard, W. A. *J. Am. Chem. Soc.* **1971**, *93*, 110.
[125] Bishop III, K. C., *Chem. Rev.* **1976**, *76*, 461.
[126] Dauben, W. G.; Kielbania, A. J., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 767.
[127] For representative reactions, see (a) Paquette, L. A. *Acc. Chem. Res.* **1971**, *4*, 280. (b) Gassman, P. G.; Atkins, T. J. *J. Am. Chem. Soc.* **1971**, *93*, 1042. (c) Gassman, P. G.; Meyer, G. R.; Williams, F. J. *J. Am. Chem. Soc.* **1972**, *94*, 7741. (d) Moriarty, R. M.; Chen, K.-N.; Flippen, J. L. *J. Am. Chem. Soc.* **1973**, *95*, 6489.
[128] (a) Noyori, R.; Suzuki, T.; Kumagai, Y.; Takaya, H. *J. Am. Chem. Soc.* **1971**, *93*, 5894. (b) Noyori, R. *Tetrahedron Lett.* **1973**, *14*, 1691. (c) Noyori, R.; Kawauchi, H.; Takaya, H. *Tetrahedron Lett.* **1974**, *15*, 1749. (d) Takaya, H.; Suzuki, T.; Kumagai, Y.; Hosoya, M.; Kawauchi, H.; Noyori, R. *J. Org. Chem.* **1981**, *46*, 2854.

Of particular interest in the context of the Simmons-Smith cyclopropanation is the reaction of bicyclobutanes with carbenes which affords 1,4-dienes **107** via a double σ-bond insertion pathway (Scheme 1.17).[118c,129,130] Since the vast majority of reactions ofbicyclobutanes occur at the central bond, it was anticipated that the reaction with a carbene would afford the corresponding bicyclo[1.1.1]pentane **106**. However, only traces of this compound were observed. Wiberg and Doering initially proposed a mechanism involving diradical intermediates, however, recent experiments and calculations support a concerted cycloaddition process.[131] Using semi-empirical MNDO calculations, the attack of methylenecarbene was found to cleave the central and side bonds simultaneously. In fact, the authors could not locate an energetic minimum corresponding to intermediates along the radical pathway. However, three transition states for the attack of singlet carbene on bicyclobutane were found. One pathway involved attack at the central bond and would lead to **106**, while the remaining transition states involved *endo*-attack of the carbene along the calculated trajectory for the protonation of bicyclobutane and afforded **107**.[132]



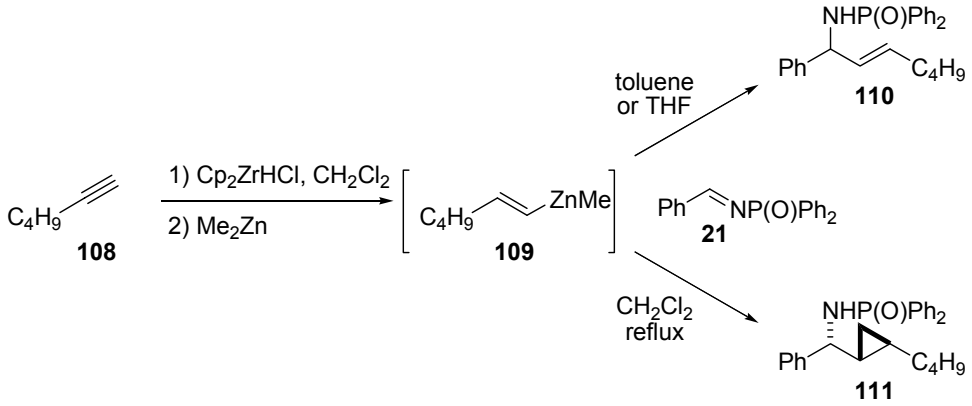
Scheme 1.17. Reaction of bicyclo[1.1.0]butanes with carbenes

[129] (a) von Doering, W.; Coburn Jr., J. F. *Tetrahedron Lett.* **1965**, *6*, 991. (b) Applequist, D. E.; Wheeler, J. W. *Tetrahedron Lett.* **1977**, *18*, 3411.
[130] For examples of single σ-bond insertion processes, see (a) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 871. (b) Murakami, M.; Itahashi, T.; Ito, Y. *J. Am. Chem. Soc.* **2002**, *124*, 13976.
[131] Jackson, J. E.; Mock, G. B.; Tetef, M. L.; Zheng, G.-X.; Jones, Jr., M. *Tetrahedron* **1985**, *41*, 1453.
[132] (a) Lehn, J. M.; Wipff, G. *J. Chem. Soc., Chem. Commun.* **1973**, 747. (b) Hoz, S. *Tetrahedron* **1984**, *40*, 5213.

1.2 Synthesis of Functionalized Allylic Amines and Alcohols

1.2.1 Dimethylzinc-Mediated Addition of Alkenylzirconocenes to Aldimines[133]

Prompted by the results of Drs. Wenjing Xu and Seth Ribe in the Wipf group, we sought to develop a method for the stereoselective preparation of allylic amides[134,135] in one-pot, using a single solvent. Since CH_2Cl_2 and THF are excellent solvents for the hydrozirconation of alkynes, these solvents were chosen as a starting point to study the alkenylzirconocene addition to imine **21** (Scheme 1.18).[136] Unfortunately, the reaction in THF did not reproducibly afford the desired allylic amine **110**, and in CH_2Cl_2 the concomitant formation of *C*-cyclopropylalkylamide **111** as a major byproduct was observed (vide infra). Fortunately, a modification of the conditions of Xu and Ribe afforded good to excellent yields of the desired allylic amide. Accordingly, after hydrozirconation in CH_2Cl_2, the solvent was removed, and the residue was dissolved in toluene and added to the imine in the presence of dimethylzinc.[137]

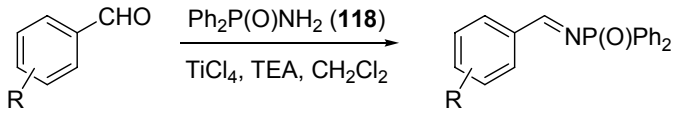


Scheme 1.18. Dimethylzinc-mediated addition of alkenylzirconocenes to imine **21**

To further probe the scope of this reaction aldehydes, **112**-**117** were condensed with phosphinamide **118** in the presence of Et_3N and $TiCl_4$ to give the functionalized aldimines **119**-

[133] Wipf, P; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2003**, *125*, 761.
[134] For the addition of alkenylzinc reagents to nitrones, see Pandya, S. U.; Garçon, C.; Chavant, P. Y.; Py, S.; Vallée, Y. *Chem. Commun.* **2001**, 1806.
[135] For a Zr→Rh transmetalation approach to allylic amides, see Kakuuchi, A.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **2003**, *44*, 923.
[136] Jennings, W. B.; Lovely, C. J. *Tetrahedron* **1991**, *47*, 5561.
[137] 1,2-Dichloroethane was also found to be an efficient solvent for allylic amine formation.

124 in poor to moderate yields (Scheme 1.19).[136] Despite the low yields obtained for these functionalized aldehydes, the reactions easily afforded sufficient material for the study of allylic amide formation.



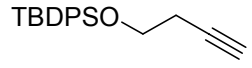
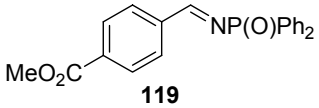
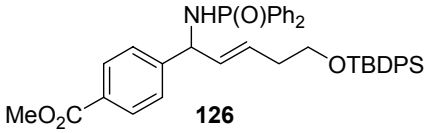
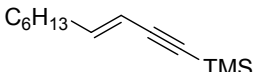
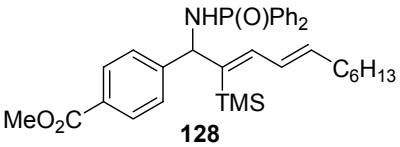
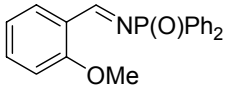
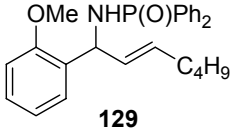
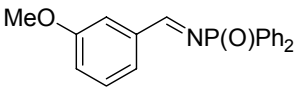
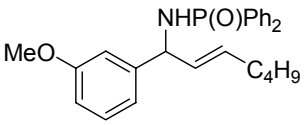
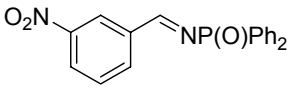
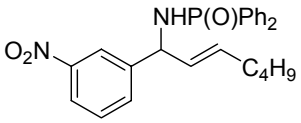
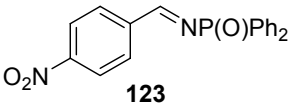
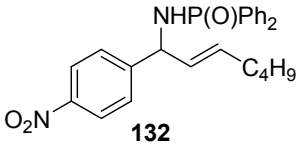
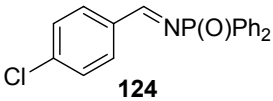
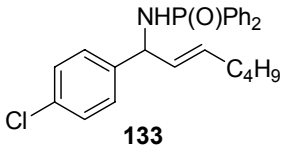
R = *p*-CO_2Me, **112**
o-OMe, **113**
m-OMe, **114**
m-NO_2, **115**
p-NO_2, **116**
p-Cl, **117**

R = *p*-CO_2Me, **119**; 54%
o-OMe, **120**; 53%
m-OMe, **121**; 29%
m-NO_2, **122**; 22%
p-NO_2, **123**; 14%
p-Cl, **124**; 37%

Scheme 1.19. Preparation of *N*-diphenylphosphinoyl aldimines

The addition of in situ generated alkenylzinc reagents to the *N*-diphenylphosphinoyl imines (**119-124**, Scheme 1.19) was undertaken in toluene. Hydrozirconation of alkynes **108**, **125** or **127** in CH_2Cl_2 followed by a solvent switch to toluene, transmetalation to zinc and addition to imine afforded the desired allylic amides in 52-82% yield (Table 1.6). Methyl esters (entries 1 and 2) and silyl ethers were tolerated under the reaction conditions as well as terminal trimethylsilyl substituted alkynes (entry 2). Electron donating groups in the *ortho*- and *meta*-position of the imine afforded the desired allylic amides in good yields, although the *para*-substituted imine (not shown) did not perform well in this reaction, affording <30% of the desired allylic amide. Interestingly, the nitro-substituted imines (entries 5 and 6) did not cause any problems during the reaction and the corresponding allylic amides were isolated in very good yields.

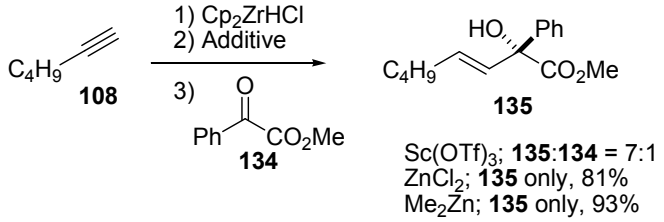
Table 1.6. Zr→Zn mediated coupling of alkynes and *N*-diphenylphosphinoylimines

entry	alkyne[a]	imine	allylic amide	yield (%)[b]
1	 **125**	 **119**	 **126**	82
2	 **127**	**119**	 **128**	52
3	**108**	 **120**	 **129**	80
4	**108**	 **121**	 **130**	66
5	**108**	 **122**	 **131**	75
6	**108**	 **123**	 **132**	73
7	**108**	 **124**	 **133**	77

[a]1.5 equiv of alkyne, Cp_2ZrHCl and Me_2Zn were employed; [b]Yield of isolated, analytically pure product based on imine

1.2.2 Dimethylzinc-Mediated Addition of Alkenylzirconocenes to α-Keto and α-Imino Esters[138]

We were motivated by the initial results of Xu[53] and Ribe[55] to probe the reactivity of alkenylzinc reagents derived from the hydrozirconation of alkynes with ketones. It became quickly apparent that these vinylzinc reagents could not be successfully employed in the direct addition to unactivated ketones.[139] We turned our attention to the more reactive α-keto esters and envisioned the possibility to use alkenylzirconocene reagents without transmetalation for the preparation of allylic alcohols (Scheme 1.20). In the absence of added Lewis acid, no conversion to the desired allylic alcohol **135** was observed. Several Lewis acids were screened as potential activators for the addition of the alkenylzirconocene derived from **108** to keto ester **134**, and several additives were capable to promote the desired reaction. However, with the exception of $ZnCl_2$,[140] conversion was low and the reaction could not be pushed to completion even with stoichiometric quantities of Lewis acid. The optimal results were obtained using conditions analogous to those developed by Xu and Ribe for the addition of alkenylzirconocenes to aldehydes.



Scheme 1.20. Activation of α-keto ester **134** with Lewis acids for the 1,2-addition of alkenylzirconocenes

The tertiary α-hydroxy carboxylates are substructures found in both natural products and pharmaceuticals.[141] The dimethylzinc-mediated addition of alkenylzirconocenes to α-keto esters proceeds smoothly in 1-2 h in 75-96% yield at r.t. providing access to important 1,2-

[138] Wipf, P.; Stephenson, C. R. J. *Org. Lett.* **2003**, *5*, 2449.
[139] Our alkenylzinc reagents failed to react with acetophenone at r.t. and upon warming afforded multiple products. The only successful ketone addition of an alkenylzinc reagent derived from an alkenylzirconocene in the absence of external Lewis acid was reported by Chavez and Jacobsen (ref. 65).
[140] Zheng, B.; Srebnik, M. *J. Org. Chem.* **1995**, *60*, 3278.
[141] (a) Comins, D. L.; Hong, H.; Saha, J. K.; Jianhua, G. *J. Org. Chem.* **1994**, *59*, 5120. (b) Senanayake, C. H.; Fang, Q. K.; Grover, P.; Bakale, R. P.; Vandenbossche, C. P.; Wald, S. A. *Tetrahedron Lett.* **1999**, *40*, 819.

dioxygenated building blocks (Table 1.7).[142] Ester functionalities were tolerated in both substrate and alkyne component, while internal alkynes (entry 2), silyl ethers (entry 3), Lewis basic benzyl ethers (entry 5) and enynes (entry 6) all successfully afforded allylic alcohols via 1,2-addition to phenyl- (entries 1-6) and methyl-substituted keto esters (entries 7 and 8). As an extension of the methodology developed for the 1,2-addition of alkenylzirconocenes to *N*-diphenylphosphinoyl imines, α-imino ester **148** was prepared (vide infra) and subjected to the vinylation conditions affording allylic amides **149** and **150** in 92% and 93% yield, respectively (entries 9 and 10).

We had hoped to be able to devlop this methodology as a catalytic asymmetric reaction. To this end, the conditions developed by Wipf and Ribe were employed to effect the asymmetric addition of the alkenylzirconocene derived from **108** to α-keto ester **134** (Figure 1.5). Unfortunately, the isolated allylic alcohol **135** was racemic in the presence of ligands **45**, **151** and **152**.[31,55] Similarly, the known Ti Lewis acids **153**[143] and **154**,[144] and bis(oxazoline) derived Lewis acids **155** and **156**[145] afforded the desired allylic alcohol; however **135** was isolated as a racemic mixture. Previous studies by Wipf and Ribe have shown that the catalyzed process was only two-fold faster than the background reaction for the vinylzinc addition to aldehydes.[55] We have qualitatively observed that α-keto esters react marginally faster than aldehydes under the Zr→Zn reaction conditions and it is possible that the background reaction simply out-competes any asymmetric pathway.

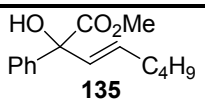
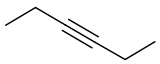
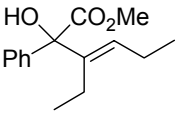
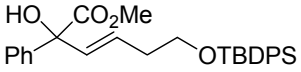
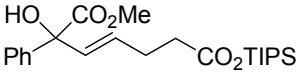
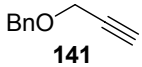
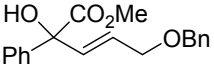
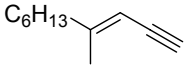
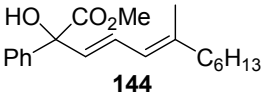
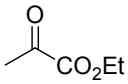
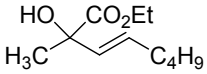
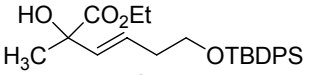
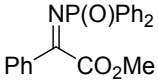
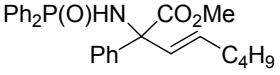
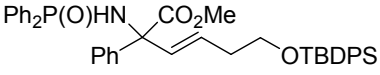
[142] (a) Akiyams, T.; Nishimoto, H.; Ishikawa, K.; Ozaki, S. *Chem. Lett.* **1992**, 447. (b) Fuji, K.; Tanaka, K.; Ahn, M.; Mizuchi, M. *Chem. Pharm. Bull.* **1994**, *42*, 957. (c) Huang, D.-L.; Draper, R. W.; Lih, D. *Tetrahedron Lett.* **1994**, *35*, 661. (d) Tamai, Y.; Nakano, T.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 439 and references cited therein.

[143] Rozema, M. J.; AchyuthaRao, S.; Knochel, P. *J. Org. Chem.* **1992**, 57, 1956.

[144] Seebach, D.; Beck, A.K.; Heckel, A. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 92.

[145] For recent reviews on the use of chiral bis(oxazoline) ligands, see (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1-45. (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325-335.

Table 1.7. Addition of alkenylzinc reagents to α-keto- and α-imino esters

entry	alkyne	keto- or imino ester	allylic alcohol or amide	yield (%)[a]
1	**108**	**134**	 **135**	93
2	 **136**	**134**	 **137**	76
3	**125**	**134**	 **138**	83
4	**139**	**134**	 **140**	82
5	 **141**	**134**	 **142**	90
6	 **143**	**134**	 **144**	88
7	**108**	 **145**	 **146**	93
8	**125**	**145**	 **147**	75
9	**108**	 **148**	 **149**	92
10	**125**	**148**	 **150**	93

[a]Yield of isolated, analytically pure product based on keto/imino ester; [b]See Scheme 1.25 for the preparation of **143**.

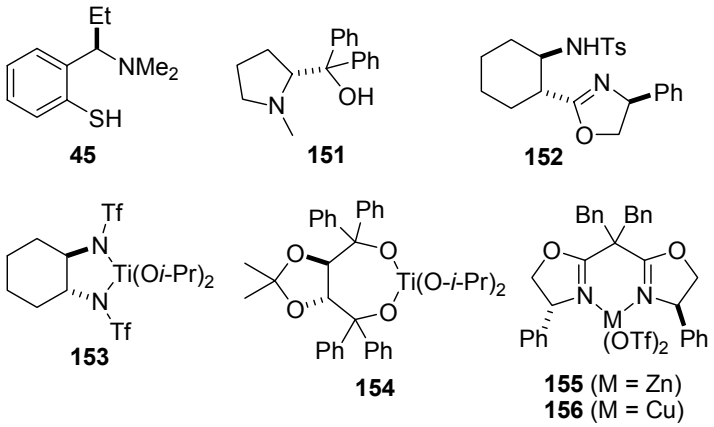
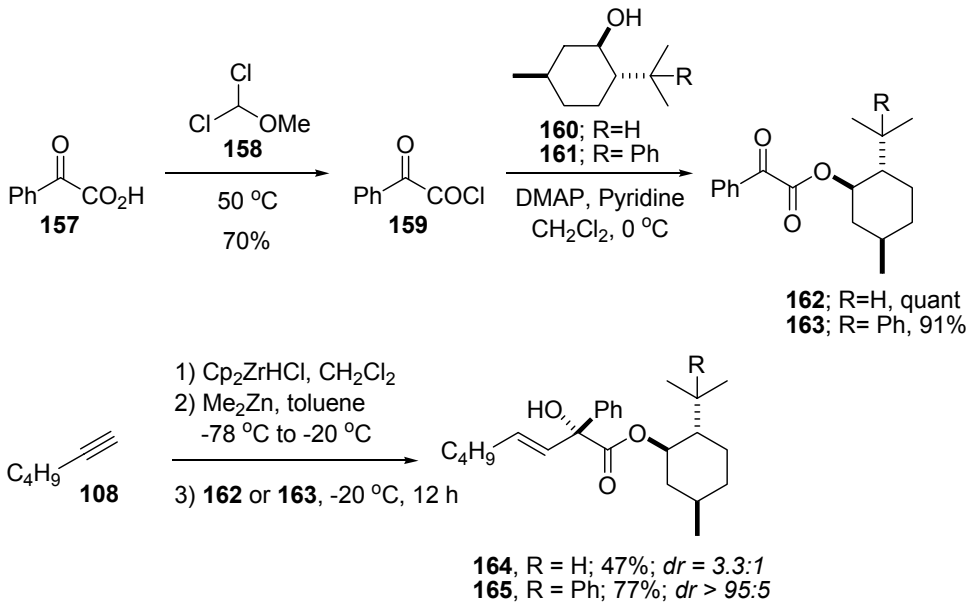


Figure 1.5. Ligands and chiral Lewis acids used in attempted asymmetric vinylzinc addition to α-keto ester **134**

Fortunately, the chelating properties of α-keto esters have been exploited for the diastereoselective addition of organometallic reagents to α-keto esters[60,146] and amides.[147] Accordingly, treatment of **158** with α,α-dichloromethylmethyl ether at 50 °C afforded **159**[148] in 70% yield[149] and the menthyl and 8-phenylmenthyl[150] keto esters **162** and **163** were prepared by condensation of the alcohols **160** and **161** with **159** in the presence of pyridine and DMAP at 0 °C in excellent yield. While the dimethylzinc-mediated addition of the alkenylzirconocene derived from **108** to the menthyl-derived keto ester **162** afforded the desired allylic alcohol with modest diastereofacial control (*dr* 3.3:1), the 8-phenylmenthyl derivative **163** afforded **165** as a single diastereomer.[151]

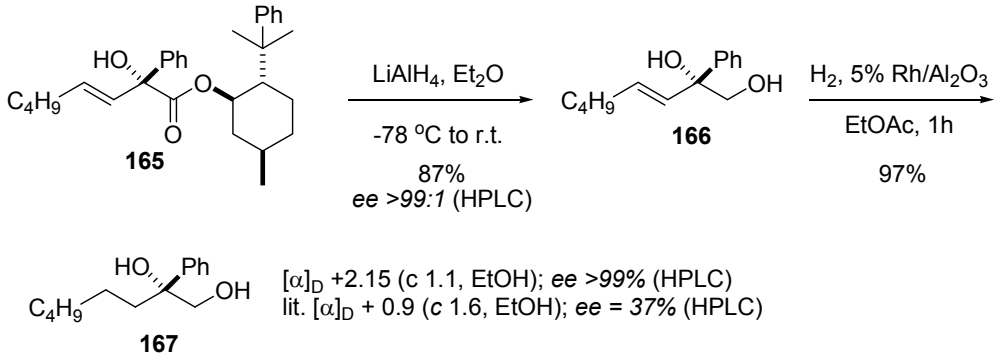
The stereochemical outcome of the addition process was verified by the preparation of the known diol **167**[152] from allylic alcohol **165**. Reduction ($LiAlH_4$, Et_2O) of **165** afforded diol **166** (87%, *ee* >99%) and recovered auxiliary **161** (92%). The minor enantiomer of **166** was not observed by HPLC analysis (Chiralcel OD).[153] Hydrogenation (H_2, Rh/Al_2O_3) afforded **167** in

[146] (a) Whitesell, J. K.; Bhattacharya, A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 988. (b) Basavaiah, D.; Bharathi, T. K. *Tetrahedron Lett.* **1991**, *32*, 3417.
[147] Kiegel, K.; Jurczak, J. *Tetrahedron Lett.* **1999**, *40*, 1009.
[148] Ottenheijim, H. C. J.; de Man, J. H. M. *Synthesis* **1975**, 163.
[149] Acid chloride **159** readily decomposes when stored at room temperature affording mixtures of **159** and benzoyl chloride. It was stored under N_2 at -20 °C and the purity was checked by ^1H NMR immediately prior to use.
[150] Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.
[151] The diastereoselectivity was determined by analysis of the crude mixture by 500 MHz ^1H NMR.
[152] Vanhessche, K. P. M.; Sharpless, K. B. *J. Org. Chem.* **1996**, *61*, 7978.
[153] See experimental section for details.



Scheme 1.21. Diastereoselective addition of alkenylzinc reagents to chiral α-keto esters **162** and **163**

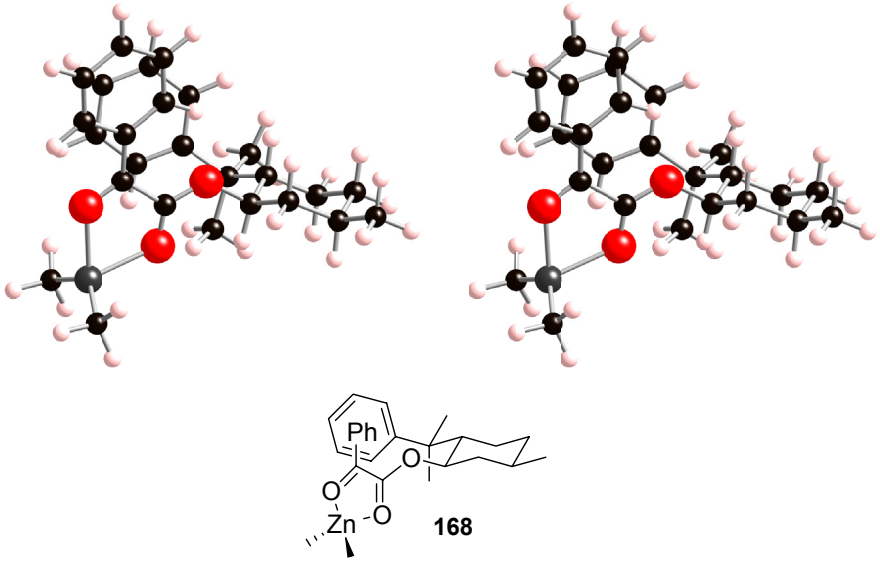
97% yield. Comparison to the literature value for the optical rotation of **167** indicated that our diol was prepared in >89% ee. However, we were unable to detect the minor enantiomer by chiral HPLC analysis (Chiralcel OD).[153]



Scheme 1.22. Verification of the absolute configuration of **165**

With the stereochemical correlation via the sign of the optical rotation of **167**, the addition was confirmed to occur onto the *si*-face of the keto ester **163** affording the allylic alcohol **165** in the (*R*)-configuration. Ab initio energy minimization (HF-6-31G*) predicted that the chelated conformation **168** shown in Figure 1.6 is at least 1.7 kcal/mol lower in energy than

any alternative conformer.[154] Included in this analysis were all mono coordinated structures where the keto ester adopts a dipole minimizing conformation of the carbonyl groups. The calculation and our observed results are also in accord with Whitesell's π-stacking model for nucleophilic additions to aryl-substituted keto esters.[60]



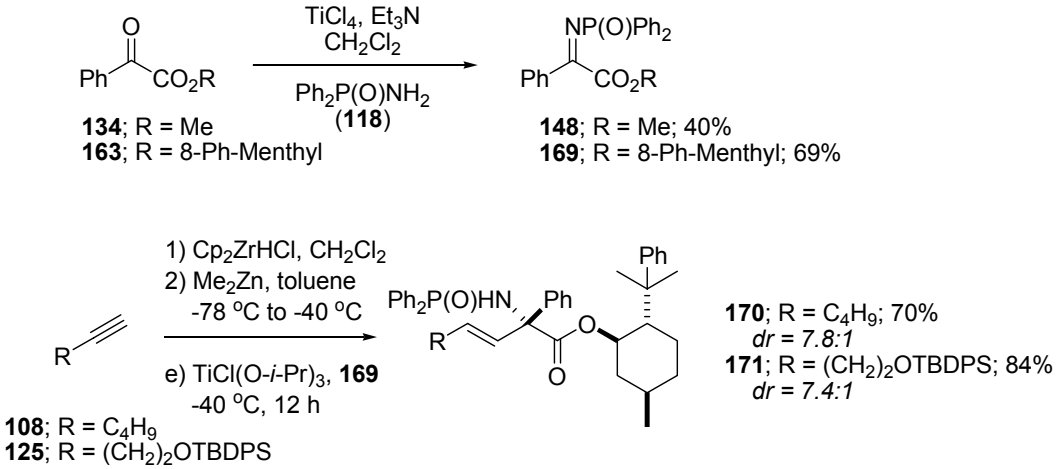
168

Figure 1.6. Stereoview of the lowest energy Me_2Zn chelated α-keto ester **168**

As shown in Table 1.7, alkenylzinc reagents can also be added to imino ester **148**, prepared in 40% yield by condensation of keto ester **134** with diphenylphosphinamide **118** in the presence of Et_3N and $TiCl_4$ (Scheme 1.23).[155] The chiral imino ester **169** was similarly prepared in 69% yield and was found to have increased stability compared to **148**. Hydrozirconation of **108** followed by transmetalation to dimethylzinc and addition to **169** afforded a disappointing 5:1 mixture of diastereomers by 600 MHz ^{1}H NMR analysis.[156] We envisioned that precomplexation of **169** with an external Lewis acid would increase the bias for the reaction occurring via a chelated structure similar to the keto ester in Figure 1.6. After a quick evaluation of Lewis acids,[157] precomplexing **169** with 1 equiv of TiCl(O-*i*-Pr)$_3$ and treatment with the

[154] The geometry was optimized by Prof. Peter Wipf using the Spartan program.
[155] The lower yield for the preparation of **148** can be attributed to facile hydrolysis during purification compared with 8-phenylmenthyl derivative **169**.
[156] Lowering the reaction temperature to -40 °C did not improve the diastereoselection and the reaction did not proceed at -78 °C, possibly due to the formation of precipitates.
[157] $ZnCl_2$, 81%, *dr 3.0:1*; $Sn(OTf)_2$, trace; $MgBr_2$, 35%, *dr 1:1*; $Zn(OTf)_2$, 65%, *dr 5.5:1*.

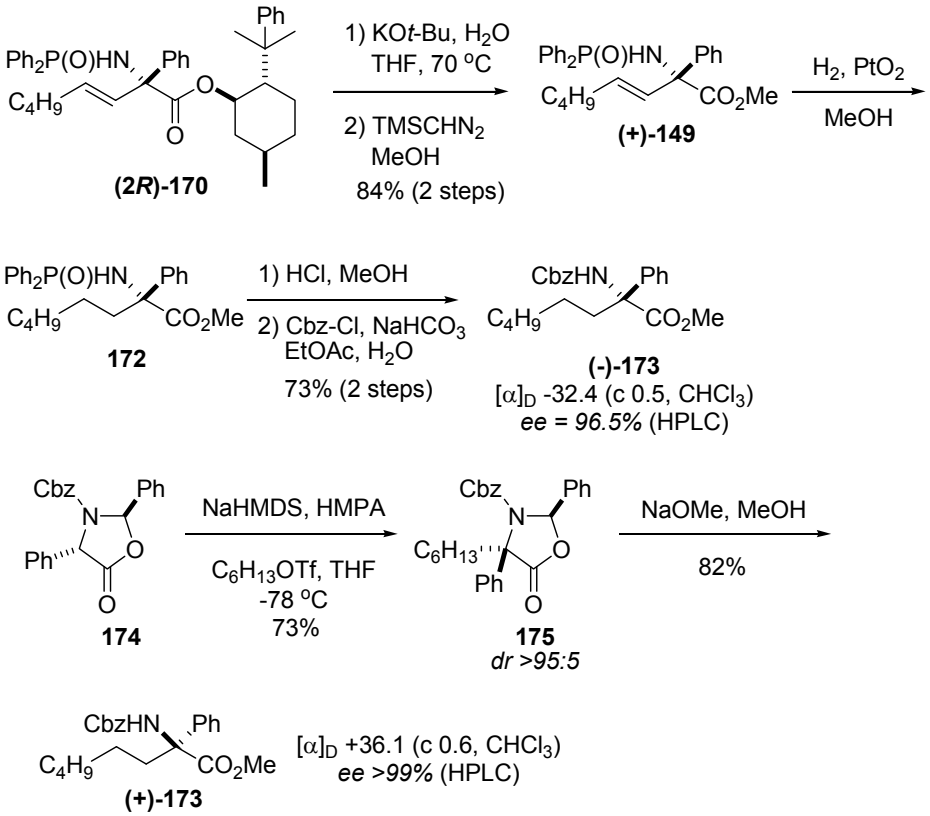
vinylzinc reagent derived from alkynes **108** and **125** at -40 °C afforded allylic amides **170** (70%; *dr = 7.8:1*) and **171** (84%; *dr = 7.4:1*) respectively in good yields and improved diastereoselectivity.



Scheme 1.23. Diastereoselective addition of alkenylzinc reagents to chiral α-imino ester **169** in the presence of TiCl(O-*i*-Pr)$_3$

The *si*-face stereoselectivity of the addition of the vinylzinc reagents was confirmed by the synthesis of amino ester (-)-**173** (Scheme 1.24). Saponification of (2*R*)-**170** (KO-*t*-Bu, H_2O, THF) followed by methylation ($TMSCHN_2$, MeOH) afforded ester (+)-**149**. Hydrogenation using Adams' catalyst (H_2, PtO_2, MeOH) afforded the saturated amino ester **172** and dephosphinoylation (HCl, MeOH) followed by Cbz protection (Cbz-Cl, $NaHCO_3$, EtOAc/H_2O) afforded the desired amino acid derivative (-)-**173**. We were able to independently prepare (+)-**173** from Cbz-*D*-Phg-OMe via oxazolidinone **174**[158] using Seebach's methodology for the self-regeneration of stereocenters.[159] Deprotonation of **174** with NaHMDS at -78 °C and treatment with freshly prepared hexyl triflate[160] in THF and HMPA afforded **175** as a single diastereomer.[161] Opening of the oxazolidinone (NaOMe, MeOH) afforded the protected amino ester, (+)-**173**. Comparison of the sign of the optical rotations permitted the assignment of the major diastereomer of the vinylzinc addition to imine **169** as the (2*R*)-stereoisomer, confirming that this addition occurs onto the *si*-face of **169** via a chelated transition state.

[158] O'Donnell, M. J.; Fang, Z.; Ma, X.; Huffman, J. C. *Heterocycles* **1997**, *46*, 617.
[159] Seebach, D.; Sting, A. R.; Hoffman, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708.
[160] Fife, W. K.; Ranganathan, P.; Zeldin, M. *J. Org. Chem.* **1990**, *55*, 5610.
[161] The diastereoselectivity was assayed by analysis of the crude ^{1}H NMR at 80 °C in DMSO-d_6.



Scheme 1.24. Confirmation of the configuration of vinylzinc adduct (2*R*)-**170**

1.3 Zirconium-Mediated Cascade Reactions of Aldimines

An interesting side reaction was observed during the addition of **174** to *N*-diphenylphosphinoylimine **30** when the reaction was attempted in CH_2Cl_2. While the expected allylic amide **110** was formed during this process, concomitant formation of *C*-cyclopropylalkylamide **111** was also observed (Scheme 1.18).[162]

1.3.1 Synthesis of *C*-Cyclopropylmethylamides by Tandem Alkenylzirconocene Aldimine Addition-Simmons Smith Cyclopropanation[133,163]

The originally developed conditions for the formation of **111** required the use of excess Cp_2ZrHCl, Me_2Zn and alkyne; however, allylic amide always remained. The addition of CH_2I_2 (5 equiv) after consumption of **21** completed the cyclopropanation reaction, affording 76% of **111**. Accordingly, a variety of *C*-cyclopropylalkylamides were prepared using this protocol with diphenylphosphinoylimines derived from substituted benzaldehydes (Table 1.8). Terminal alkynes (entries 1, 3-7) and unsymmetrical internal alkynes (entry 2) perform well in this reaction. Electron withdrawing (entries 3-5) and donating (entry 6) substituents were accommodated in the reaction affording the desired amino cyclopropanes. Interestingly, the *ortho*-methoxy substituted imine **120** afforded a mixture of *C*-cyclopropylalkylamide **184** and allylic amide **129** despite attempts to force the reaction to completion.[164] This three-component condensation can also be scaled up to afford preparatively useful quantities of *C*-cyclopropylalkylamides. For example, **177** was prepared in 75% yield (3.1 mmol of **21**) and 55% (11.5 mmol of **21**), while the reaction with internal alkyne **178** afforded 61% of *C*-cyclopropylalkylamide **179** (5.9 mmol of **21**).

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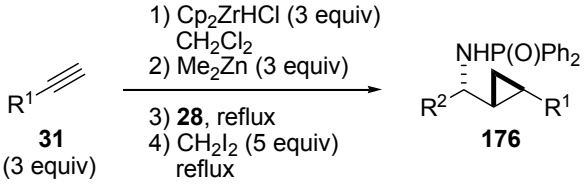
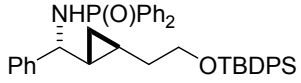
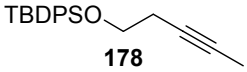
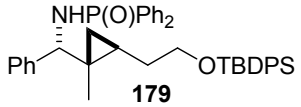
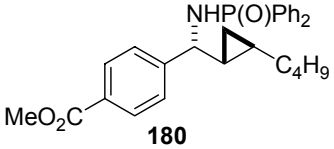
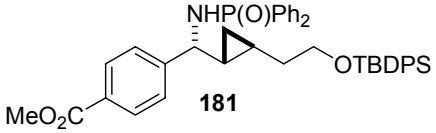
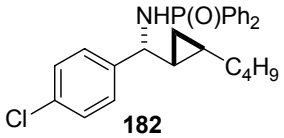
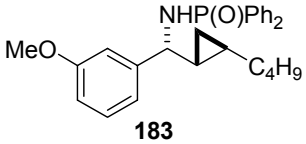
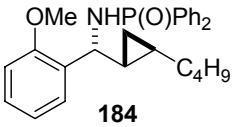
[162] The cyclopropane product was first observed by Dr. Christopher Kendall. Traces of this product are also observed in reactions carried out in toluene or $Cl(CH_2)_2Cl$ due to residual CH_2Cl_2 from the hydrozirconation process.

[163] Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2003**, *125*, 761.

[164] Prolonged reaction times at reflux in CH_2Cl_2 or an additional portion of CH_2I_2 (5 equiv) did not significantly affect this transformation.

Table 1.8. Synthesis of *C*-cyclopropylalkylamides via a three-component condensation



entry	alkyne	imine	*C*-cyclopropylalkylamide	yield (%)[a]
1	**125**	**21**	 **177**	75 (55)[b]
2	 **178**	**21**	 **179**	61[c]
3	**108**	**119**	 **180**	69
4	**125**	**119**	 **181**	84
5	**108**	**124**	 **182**	65
6	**108**	**121**	 **183**	51
7	**108**	**120**	 **184**	32[d]

[a]Yield of isolated, analytically pure product based on imine; [b]3.5 g of imine; [c]1.8 g of imine;
[d]A mixture of allylic- and *C*-cyclopropylalkylamide was isolated (**184**:**129** = 1:1.7)

The observed *anti*-diastereoselectivity[165] can be explained using a model akin to those proposed for the Simmons-Smith cyclopropanation of allylic ethers (Figure 1.7). For R ≠ H, the $A^{1,3}$-strain-minimized[166] transition state **A** predominates for the cyclopropanation of allylic

[165] The diastereoselectivity was confirmed by X-ray crystallographic analysis of the benzamide derivative of **111** prepared by Dr. Chris Kendall. See (a) ref. 163. (b) Kendall, C. Ph.D Dissertation, University of Pittsburgh, 2004.
[166] Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841.

amides, leading to the *syn*-diastereomer **185** (vide infra). However, for R = H, the repulsive interactions of the bulky nitrogen protective group with the olefin control the facial attack, and transition state **B** is preferred leading to the observed *anti*-diastereomer **186**.

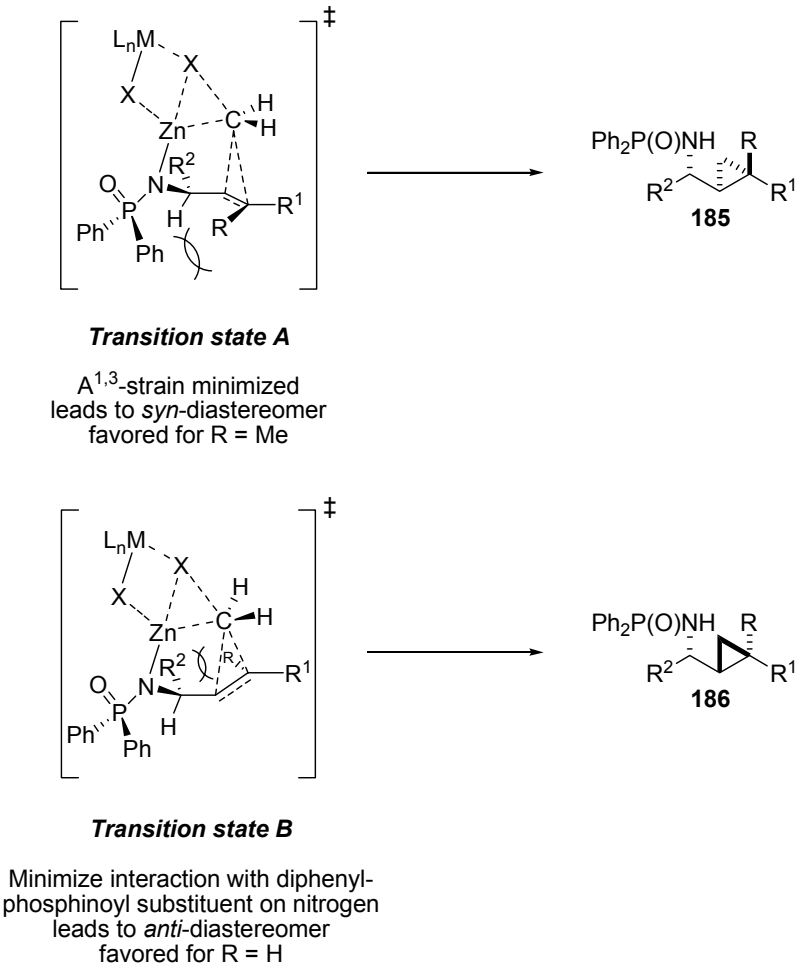


Figure 1.7. Proposed transition states leading to *syn*- or *anti*-*C*-cyclopropylalkylamides

As an extension of this new methodology for the stereoselective preparation of *C*-cyclopropylalkylamides, we wanted to examine if vinylcyclopropanes could be easily prepared under these conditions. Vinylcyclopropanes could prove to be valuable starting materials for the preparation of amino acids (See Chapter 2) or for application in higher order cycloaddition chemistry, providing rapid access to building blocks previously available only via multi-step

synthesis.[167] In order to examine this possibility, we chose to prepare enyne **143**. Water-accelerated carboalumination of **55** followed by iodination afforded the vinyl iodide **187** in 85% yield (Scheme 1.25).[168] Sonagashira coupling[169] with **188** ($Pd(PPh_3)_4$, CuI, *i*-Pr_2NH) and desilylation (TBAF, THF/MeOH) afforded **143** in excellent yield (80%, 3 steps). Under the standard reaction conditions developed for *C*-cyclopropylalkylamide formation (3 equiv **189**, Cp_2ZrHCl and Me_2Zn), bicyclopropane **190** was isolated as a single diastereomer in 70% yield. Unfortunately, we were unable to determine the relative configuration of this sample since crystals suitable for x-ray diffraction analysis could not be grown for **190** or simple amide deriviatives. In hopes of overcoming this problem, **195** was prepared in an analogous fashion beginning with the carboalumination of 3-butyn-1-ol.[170] TBDPS-protection (TBDPS-Cl, Imid) and Sonagashira coupling with **188** ($Pd(PPh_3)_4$, CuI, *i*-Pr_2NH) followed by *C*-desilylation (K_2CO_3, MeOH) afforded **195**. Under otherwise identical conditions, the second cyclopropanation was more sluggish for this enyne. However, the reaction could be driven to completion with the use of excess CH_2I_2 (3 x 5 equiv) to afford the desired bicylopropane **196** in 53% yield. Desilylation (TBAF, AcOH) afforded alcohol **197** which was crystallized from Et_2O by slow evaporation to afford crystals suitable for diffraction studies. The reaction proceeded to afford the *anti*-*anti*-diastereomer of bicyclopropane **196** (Figure 1.8).

While the *anti*-relationship between the amide and the proximal cyclopropane was expected based on our model for the cyclopropanation of simple allylic amides (Figure 1.7), a rational explanation for the *syn*-stereoselectivity for the cyclopropanation of the distal olefin was not immediately obvious.[171] However, given the elongated N-Zn and C-Zn bonds (ca. 2 Å),[172] intramolecular delivery of the carbenoid remains feasible despite the *trans*-cyclopropane present in the 8-membered ring. Assuming that the compound must fold into a conformation such that

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[167] (a) Wender, P. A.; Rieck, H.; Fuji, M. *J. Am. Chem. Soc.* **1998**, *120*, 10976. (b) Trost, B.M.; Toste, F.D.; Shen, H. *J. Am. Chem. Soc.* **2000**, *122*, 3534.

[168] (a) Wipf, P.; Lim, S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068. (b) Ribe, S.; Wipf, P. *J. Chem. Soc., Chem. Commun.* **2001**, 299.

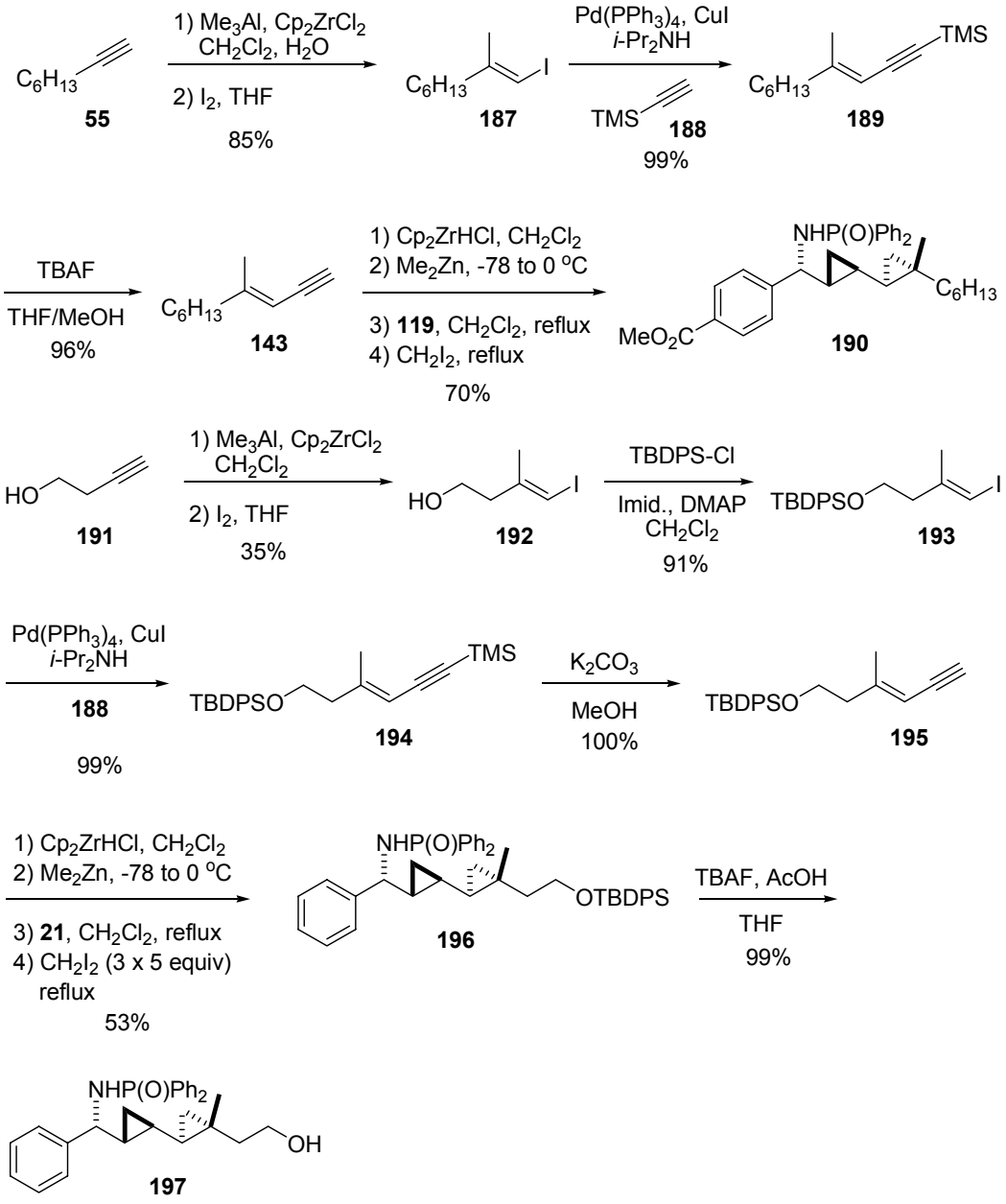
[169] Sonagashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.: Wiley-VCH: New York, 1998; p 203.

[170] Negishi, E.; Takahashi, T. *Synthesis* **1988**, 1.

[171] Intermolecular cyclopropanation was ruled out based upon control experiments in which alkenes which were added to the reaction did not undergo cyclopropanation.

[172] For C-Zn and N-Zn bond lengths taken from x-ray structures of zinc carbenoids see (a) C-Zn; Charette, A. B.; Marcoux, J.-F.; Molinaro, C.; Beauchemin, A.; Brochu, C.; Isabel, E. *J. Am. Chem. Soc.* **2000**, *122*, 4508. (b) N-Zn; Denmark, S. E.; O'Connor, S. P.; Wilson, S. R. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1149. (c) See also ref. 87.

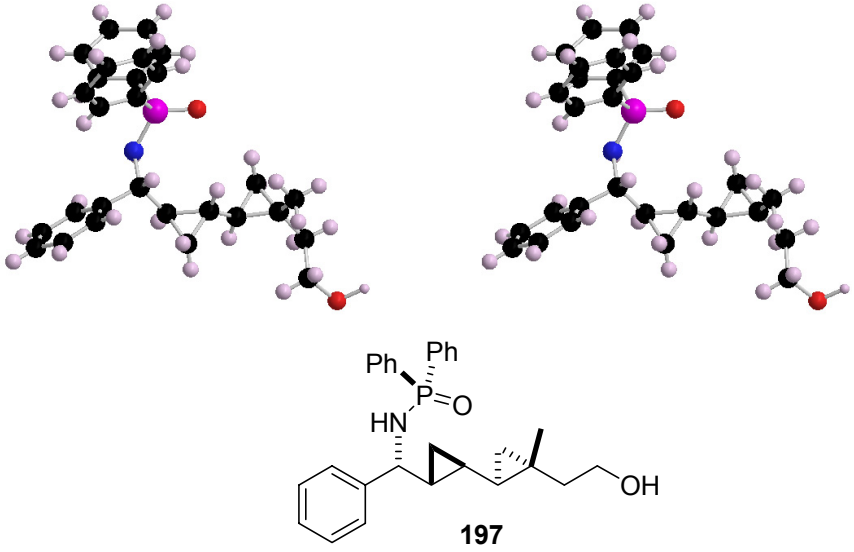
the reaction occurs with the proximal cyclopropane outside of the 8-membered ring, then two limiting transition states must be considered (Figure 1.9). In transition state **A**, the vinylcyclopropane is extended in the *s-trans* conformation (minimizing $A^{1,3}$-strain) and the eight-membered ring folds into a chair conformation, delivering the carbenoid to the *re*-face of the olefin and affording the observed *anti-anti*-diastereomer **198**. Conversely, the *anti-syn*-



Scheme 1.25. Synthesis of bicyclopropanes from aldimines and enynes using the Zr→Zn methodology for *C*-cyclopropylalkylamide formation

diastereomer must be formed by delivery to the *si*-face of the olefin. Accordingly, the vinylcyclopropane must adopt an *s-cis*-conformation (transition state **B**), forcing unfavorable non-bonded interactions between the methyl group of the olefin and the pseudo axial hydrogen of the cyclopropane. The observed diastereoselectivity is in excellent accord with the results of Barrett and co-workers for the cyclopropanation of dienyl alcohols and ethers.[101]

The methodology developed herein has been successfully applied to the preparation of novel cyclopropane-containing amino acids and to initiate β-turns[173] or stabilize extended structures, such as β-sheet mimetics.[174]



197

Figure 1.8. Stereoview of the x-ray crystal structure of **197** generated using Chem3D[175]

[173] Wipf, P.; Xiao, J. *Org. Lett.* **2005**, *7*, 103.
[174] See Chapter 2 for details.
[175] See Appendix A for crystal coordinates.

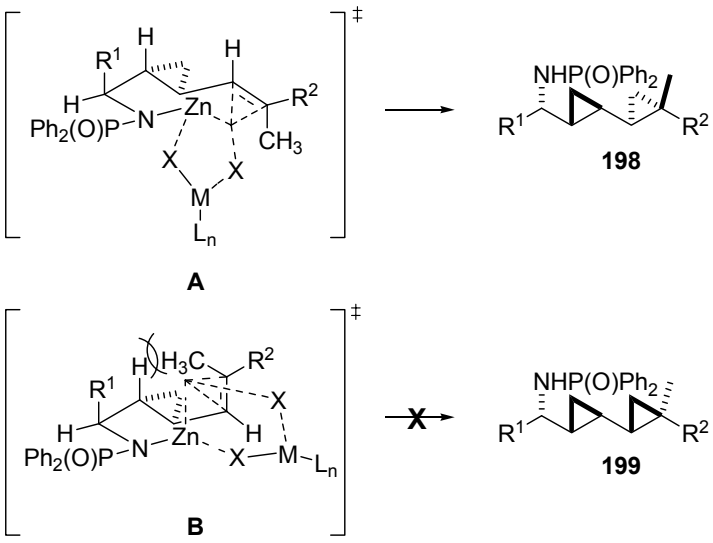


Figure 1.9. Proposed transition state for the diastereoselective formation of bicyclopropanes from enynes and aldimines

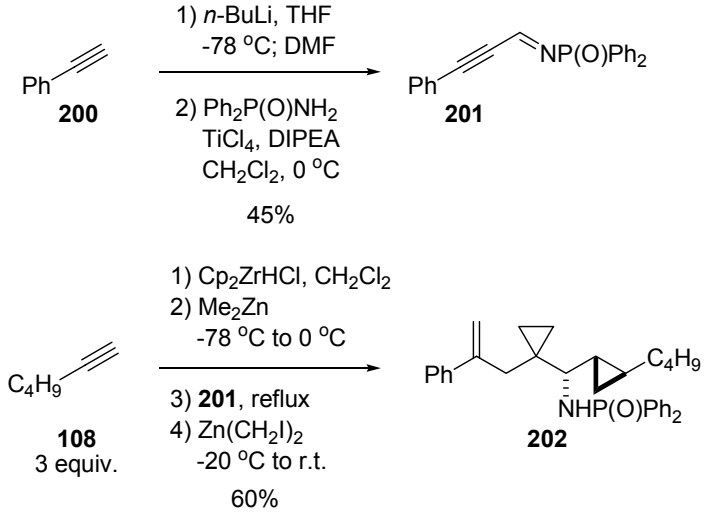
1.3.2 Synthesis of *C*,*C*-Dicyclopropylmethylamides by Double C,C-σ-Bond Insertions into Bicyclobutanes[176]

During the course of our studies towards the preparation of cyclopropyl amino acids using our Zr→Zn methodology, we found that propargyl ethers such as **141** did not afford *C*-cyclopropylalkylamides. Fortunately, we were able to use $Zn(CH_2I)_2$ in place of CH_2I_2 for these less reactive substrates (vide infra). The application of this protocol during the dimethylzinc-mediated addition of the alkenylzirconocene derived from **108** to alkynyl imine **201**[163] afforded *C*,*C*-dicyclopropylmethylamide **202** in 60% yield as a single diastereomer (Scheme 1.26).[177] In the course of this remarkable cascade process, ten new C,C-bonds were formed, while two C,C-bonds were broken, including the alkyne triple bond of the imine.

One of the disadvantages of our methodology for the preparation of *C*-cyclopropylalkylamides[163] is that a three-fold excess of the alkenylzinc reagent (alkyne, Cp_2ZrHCl and Me_2Zn) is required.[178] We briefly examined conditions to optimize the formation of **202**, while attempting to decrease the amount of zirconium, zinc and alkyne (Table 1.9).

[176] Wipf, P.; Stephenson, C. R. J.; Okumura, K. *J. Am. Chem. Soc.* **2003**, *125*, 14694.
[177] The structure of a related *C*,*C*-dicyclopropylmethylamide was fully assigned using 2D-NMR techniques.
[178] The lifetime of the vinylzinc reagent prepared under these conditions is significantly shorter in CH_2Cl_2 than toluene. Wipf, P.; Kendall, C., Unpublished results. For a related study on the stability of vinylzinc reagents prepared from B→Zn transmetalation, see ref. 64a.

Switching solvents from CH_2Cl_2 (entry 1) to toluene or chlorobenzene (entries 2 and 3) permitted the use of only 1.5 equiv of the vinylzinc reagent as the reaction proceeded smoothly to afford the intermediate allylic amide. However, these solvents appear to be incompatible with the conditions for the second step of the reaction resulting in lower isolated yields of **202**. A similarly non-polar solvent, dichloroethane, also was useful for the addition to *N*-diphenylphosphinoyl imines (vide supra) and is generally regarded as an ideal solvent for the Simmons-Smith cyclopropanation reaction.[91] Accordingly, the multi-component condensation in dichloroethane with 4 equiv of $Zn(CH_2I)_2$ afforded 60% (entry 4) of **202**. Lowering the reaction temperature to 0 °C improved the yield slightly to 68% (entry 5). While the improvements achieved in the reaction yield were modest at best, the overall transformation is superior as we now require significantly less organometallic reagent for an equivalent transformation.



Scheme 1.26. Multi-component synthesis of *C*,*C*-dicyclopropylmethylamide **202** from imine **201**, alkyne **108** and $Zn(CH_2I)_2$

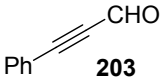
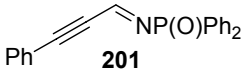
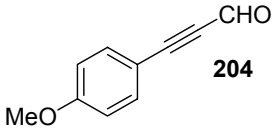
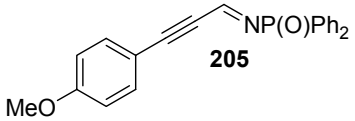
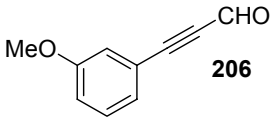
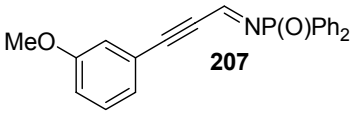
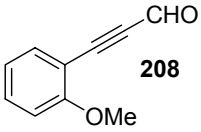
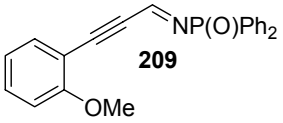
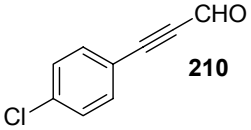
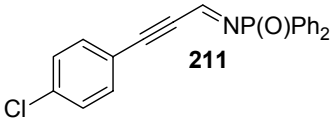
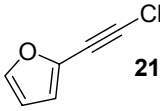
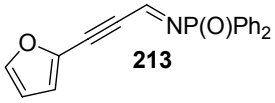
A selection of *N*-diphenylphosphinoylalkynylimines was prepared according to a modification of a literature procedure (Table 1.10).[136] A variety of electron-rich (entries 2-4), electron-poor (entry 5) and heterocyclic (entry 6) imines were prepared. In all cases, the isolated yield was low to modest although the reactions could easily be scaled up to afford gram quantities of imine. In the case of entry 6, the imine readily decomposed during purification and was used in the subsequent reaction without extensive purification.

Table 1.9. Optimization of the formation of **202** from alkyne **108** and imine **201**

entry	equiv of Cp_2ZrHCl	equiv of **108**	equiv of Me_2Zn	equiv of $Zn(CH_2I)_2$	solvent	temp (°C)	yield (%)[a]
1	3	3	3	3	CH_2Cl_2	r.t.	60
2	1.5	1.5	1.5	4	toluene	r.t.	<50
3	1.5	1.5	1.5	4	C_6H_5Cl	0	46
4	1.5	1.5	1.5	4	$Cl(CH_2)_2Cl$	r.t.	60
5	1.5	1.5	1.5	4	$Cl(CH_2)_2Cl$	0	68

[a]Yield of isolated, analytically pure product based on imine.

Table 1.10. Preparation of alkynyl imines from aryl-substituted propynals

entry	aldehyde[179]	imine	yield (%)[a]
1	 **203**	 **201**	45
2	 **204**	 **205**	49
3	 **206**	 **207**	21
4	 **208**	 **209**	50
5	 **210**	 **211**	36
6	 **212**	 **213**	24[b]

[a]Yield of isolated, analytically pure product based on aldehyde;[180] [b]Imine was used without further purification

[179] The aldehydes were prepared from the corresponding teminal acetylene (*n*-BuLi, THF, then DMF) and were used without extensive purification.

[180] We did not rigourously attempt to optimize the yield of imine formation.

The functionalized imines were subjected to the optimized reaction conditions for *C*,*C*-dicylopropylmethylamide formation (Table 1.11). While the parent imine **201** afforded **202** in good yield, electron-donating (entries 2-4), electron-withdrawing (entry 5) and hetrocyclic imines (entry 6) were well tolerated, affording the corresponding *C*,*C*-dicyclopropylmethyl-amides in 47-58% yield. The variation in the alkyne portion follows the general reactivity principles of alkenylzirconocenes and it was not surprising that alkynes bearing silyl ethers (entry 7), silyl and ortho esters[181] (entries 8 and 9) as well as sulfonamides and carbamates afforded the *C*,*C*-dicyclopropylmethylamides in 43-55% yield. For the preparation of **219** on >1 mmol scale, $Zn(CH_2I)_2$•DME complex[182] was substituted for $Zn(CH_2I)_2$ without noticeable attenuation in reactivity despite the presence of the deactivating DME ligand. While the overall yield in this transformation is moderate, the yield per C,C-bond forming event (6) is excellent (87-94%).[183]

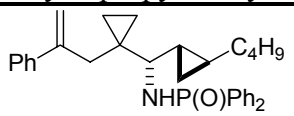
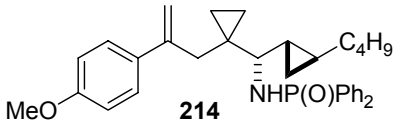
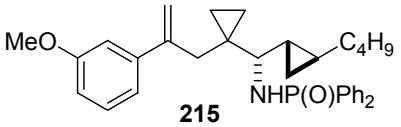
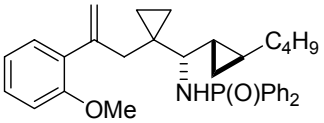
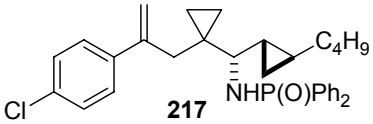
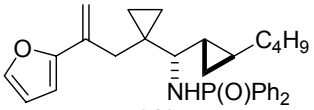
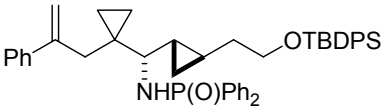
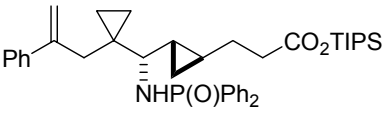
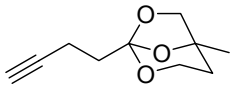
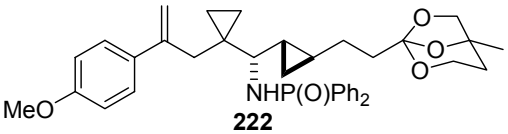
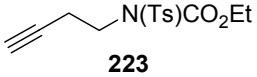
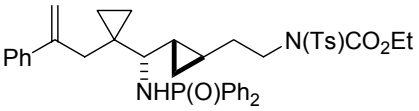
As part of our studies to better understand the reaction of propargyl amides with zinc carbenoids, model propargylic amides **226** and **228** were prepared. *N*-Protection of propargyl amine followed by Sonagashira coupling[169] afforded the unsubstituted propargyl phosphinamide **226**. Treatment of a solution of **226** in CH_2Cl_2 or $Cl(CH_2)_2Cl$ with $Zn(CH_2I)_2$ did not result in any conversion to **227**. However, stirring **226** with Me_2Zn followed by treatment with $Zn(CH_2I)_2$ afforded 61% of *C*-cyclopropylalkylamide **227**. This result was intriguing since allylic amides are cyclopropanated without pre-treatment with an alkylzinc reagent.[133] Similarly, allylic amide **228** was prepared using the Zr→Zn methodology and subjected to the rearrangement conditions affording **202** in 72% yield. This important extension of the methodology allows for an increase in the diversity of structures available as the reaction cascade no longer must be initiated by an imine alkenylation event.

[181] (a) Wipf, P.; Xu, W. *J. Org. Chem.* **1993**, *58*, 5880. (b) Wipf, P.; Xu, W.; Kim, H.; Takahashi, H. *Tetrahedron* **1997**, *53*, 16575.

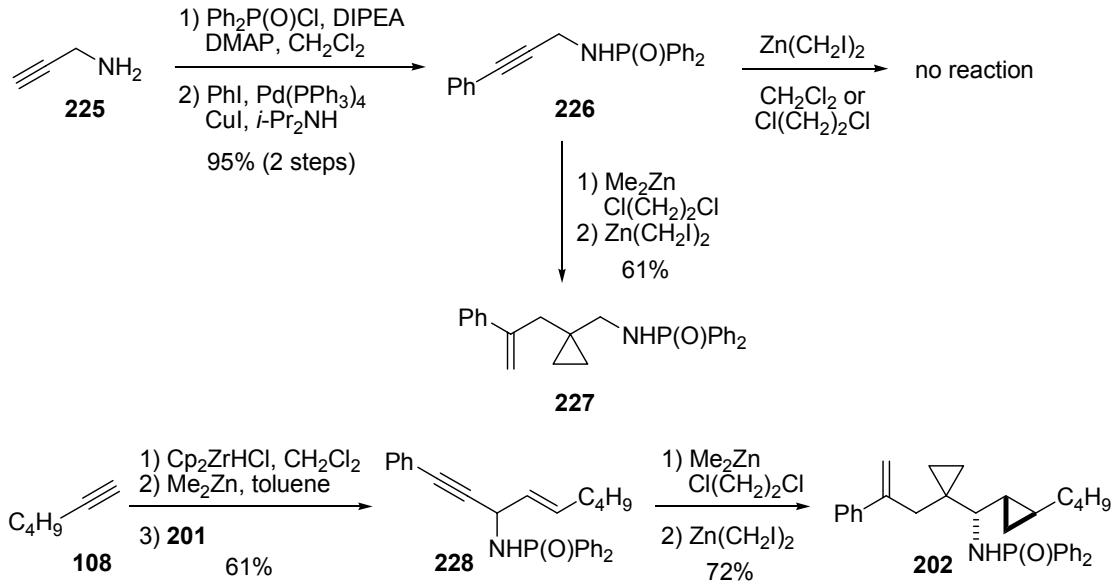
[182] The reaction of Et_2Zn with CH_2I_2 is very exothermic and explosions have been observed in the Charette lab. They have suggested the use of the DME complex as a safe alternative to $Zn(CH_2I)_2$ for reactions requiring >1 mmol of zinc carbenoid. For details, see ref. 108b.

[183] The formation of a cyclopropane during this process has been counted as one bond forming event.

Table 1.11. Synthesis of *C*,*C*-dicyclopropylmethylamides via the Zr→Zn initiated multi-component condensation reaction

entry	alkyne	imine	*C*,*C*-dicyclopropylmethylamide	yield (%)[a]
1	**108**	**201**	 **202**	68
2	**108**	**205**	 **214**	50
3	**108**	**207**	 **215**	50
4	**108**	**209**	 **216**	52
5	**108**	**211**	 **217**	58
6	**108**	**213**	 **218**	47
7	**125**	**201**	 **219**	55[b]
8	**139**	**201**	 **220**	55
9	 **221**	**205**	 **222**	44
10	 **223**	**201**	 **224**	43

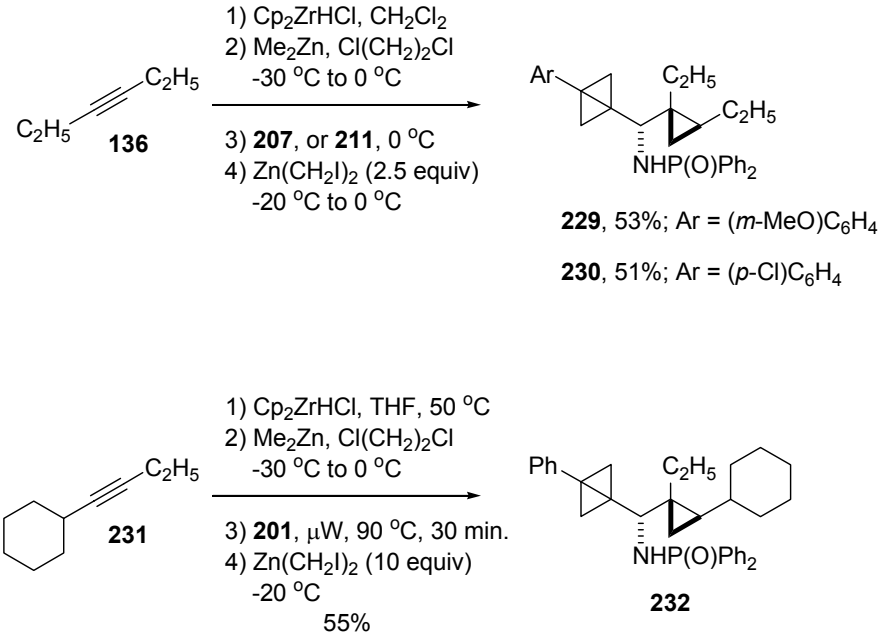
[a]Yield of isolated, analytically pure product based on imine; [b]$Zn(CH_2I)_2$•DME complex used in place of $Zn(CH_2I)_2$



Scheme 1.27. Synthesis of *C*,*C*-dicyclopropylalkylamides from propargyl phosphinamides

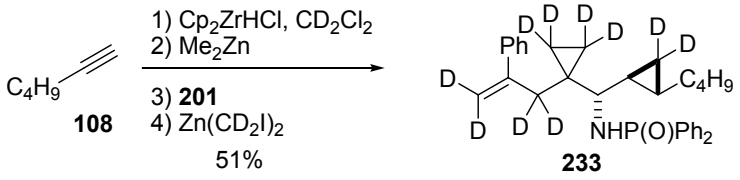
Examing further the scope of the reaction to include internal alkynes precipitated a fortuitous result; the reaction of **136** with **211** under our standard rection conditions afforded bicyclobutane **229** as the major product and the expected *C*,*C*-dicylopropylmethylamide was not observed (Scheme 1.28).[184] Decreasing the amount of zinc carbenoid (4 to 2.5 equiv) resulted in cleaner conversion to the bicyclo[1.1.0]butane product **229**. In fact, both electron-withdrawing (*p*-ClC_6H_4) and -donating (*m*-$MeOC_6H_4$) aryl-substituted bicyclo[1.1.0]butanes could be easily prepared using this protocol. Initially, we had difficulty generating the alkenylzinc reagent of the unsymmetrical, internal alkyne **231** due to an unselective hydrometalation event. Using the protocol developed by Panek,[23] **231** was hydrozirconated in THF at 50 °C; yet the addition to **201** was extrememly sluggish at 0 °C or even r.t.[185] Fortunately, the use of microwave irradiation (90 °C for 30 min) resolved this problem and treatment of the intermediate allylic amide with 10 equiv of $Zn(CH_2I)_2$ at -20 °C afforded the desired bicyclo[1.1.0]butane in 55% yield.[186]

[184] Traces of alkene containing products were removed by treatment of the crude reaction mixture with OsO_4/NMO.
[185] The reaction did not reach completion even after 24 h at r.t.
[186] The more hindered cyclohexyl substituent seems to greatly affect the reactivity of the olefin under the cyclopropanation conditions and excess reagent was used. However, at elevated temperatures, the excess reagent also promoted the conversion of the bicyclo[1.1.0]butane to the corresponding *C*,*C*-dicyclopropylmethylamide.



Scheme 1.28. Synthesis of bicyclo[1.1.0]butanes from alkynyl imines and internal alkynes

Before postulating a mechanism to account for the formation of *C*,*C*-dicyclopropylalkyl-amides in this cascade process, isotopic labeling was performed in the reaction of **108** with **201**. Hydrozirconation of **108** in CD_2Cl_2 (3 equiv alkyne, Cp_2ZrHCl), transmetalation to zinc (3 equiv Me_2Zn) and addition to the **201** (CD_2Cl_2, reflux) followed by treatment with $Zn(CD_2I)_2$ afforded the deuterated derivative **233** in 51% yield.



Scheme 1.29. Isotopic labelling studies: Synthesis of deuterated *C*,*C*-dicylopropylalkylamide **233**

On the basis of the evidence that we have gathered thus far, the mechanism for the formation of *C*,*C*-dicyclopropylmethylamides outlined in Figure 1.10 is proposed. The Zr→Zn methodology affords the metalated allylic amide **236**. Alkyl group exchange upon treatment with $Zn(CH_2I)_2$ followed by a nitrogen-directed Simmons-Smith cyclopropanation gives the

amino cyclopropane **238**. With excess zinc carbenoid, the alkyne is now cyclopropanated twice to afford the bicyclobutane **242** via the proposed cyclopropene intermediate **241**. As we have already demonstrated, the bicyclo[1.1.0]butane intermediate can be isolated when internal alkynes are used in this reaction cascade. These reactive intermediates have been shown to undergo double σ-bond insertion reactions with carbenes to afford the skipped diene **244**.[118,131] The net result of this insertion is the scission of the C1-C3 and C1-C4 bonds and the formation of a 1,1-disubstituted olefin between C1 and C5. Finally, Simmons-Smith cyclopropanation of the proximal olefin affords the *C*,*C*-dicyclopropylmethylamide **247** after work up.[187]

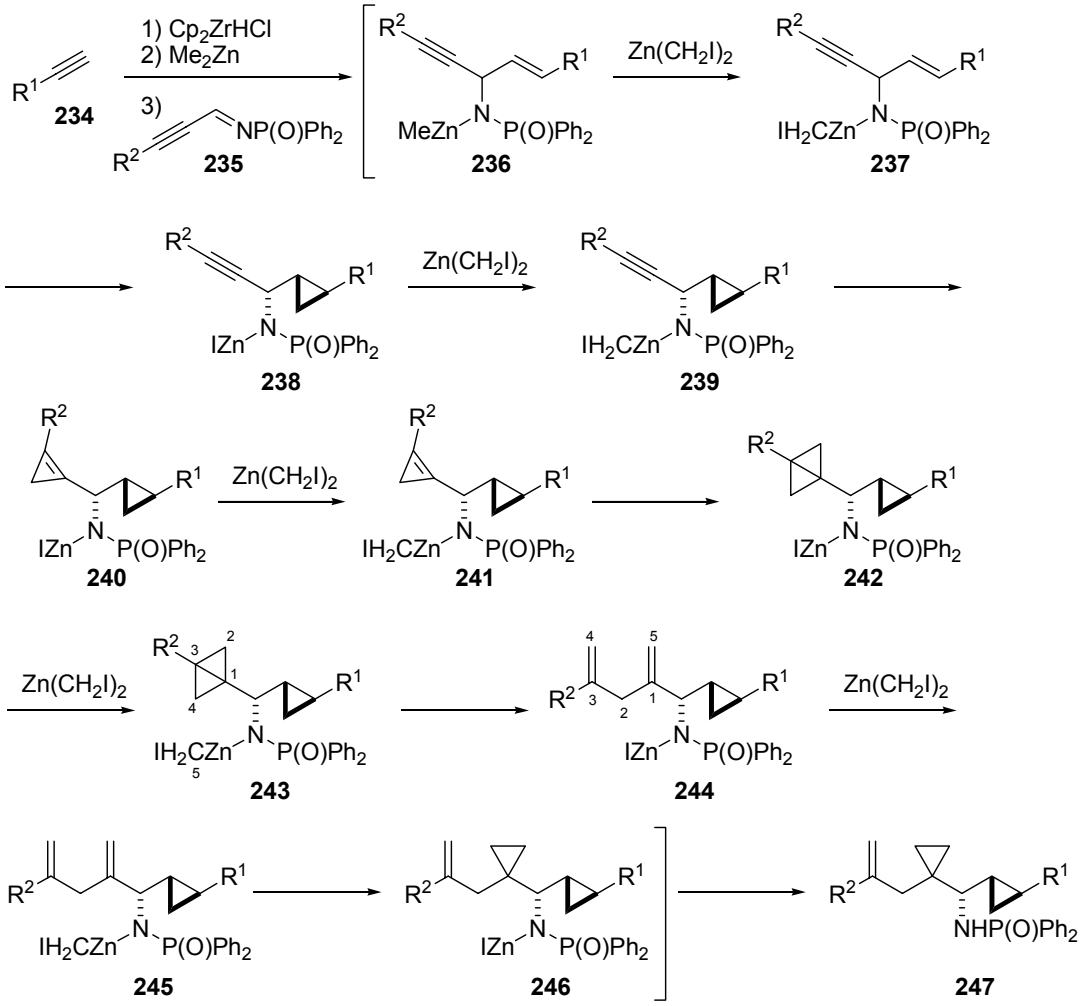


Figure 1.10. Proposed mechanism for the formation of dicyclopropylmethylamides

[187] Upon prolonged exposure, and particularly in the case of electron rich aromatics, the styrenyl olefin may also react with the carbenoid.

1.3.3 Synthesis of Functionalized Azaspirocycles from *C*,*C*-Dicyclopropylmethylamides[188]

While the *C*,*C*-dicyclopropylmethylamide scaffold is interesting in itself for further biological evaluation, the flexible nature of these compounds raises issues with metabolism and bioavailability.[189] In order to address this issue, we targeted 5-, 6-, and 7-membered nitrogen-containing heterocycles to expand the structural diversity of these new building blocks.[190] *N*-Alkylation of **248** on nitrogen followed by ring closing metathesis[191,192,193] was presumed to afford the desired azepines **250** (Table 1.12).[194] Upon deprotonation of **248** with NaH, no alkylation with allyl iodide was observed at r.t., and on warming to 70 °C, conversion to the *N*-allylated product **249** was slow. Treatment of the anion with HMPA followed by allyl iodide and heating at 70 °C resulted in clean conversion to the desired alkylated intermediates **249** in good to excellent yields in 1-2 h. Following a literature protocol for the preparation of azepines using ring closing metathesis in refluxing $Cl(CH_2)_2Cl$ (bp 83 °C),[194d] **249** was rapidly consumed, however, alkene isomerization to the enamide prior to cyclization was competitive with ring-closing to azepine **250** (enamide:azepine ~1:1).[194c,195] A simple change in solvent to CH_2Cl_2 (bp 40 °C) minimized the isomerization pathway[196] leading to the desired azepines in 63-84% yield.

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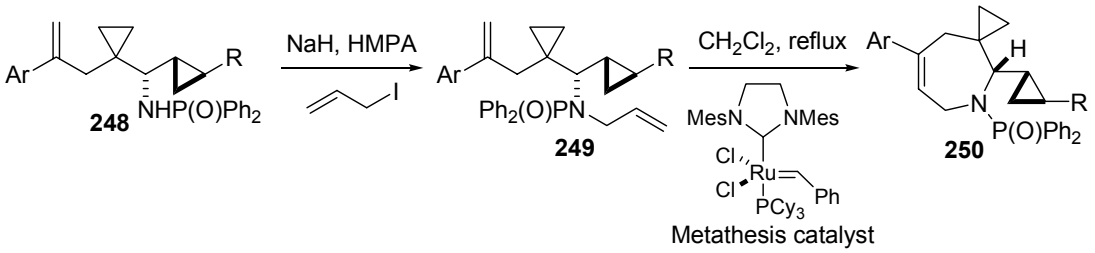
[188] Wipf, P.; Stephenson, C. R. J.; Walczak, M. A. A. *Org. Lett.* **2004**, *6*, 3009.
[189] Veber, D. F.; Johnson, S. R.; Cheng, H.-Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. *J. Med. Chem.* **2002**, *45*, 2615.
[190] For short reviews on diversity-oriented synthesis, see (a) Spring, D. R. *Org. Biomol. Chem.* **2003**, *1*, 3867. (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 46.
[191] For some recent reviews on ring closing metathesis, see (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Furstner, A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3012.
[192] For a recent review on the formation of nitrogen-containing heterocycles by ring closing metathesis, see Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.
[193] For discussion of the mechanism of Ru-based ring-closing metathesis reactions, see (a) Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749. (b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.
[194] For the preparation of azepines by ring closing metathesis, see (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324. (b) Furstner, A.; Guth, O.; Duffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R. *Chem. Eur. J.* **2001**, *7*, 4811. (c) Wipf, P.; Rector, S.; Takahashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 14848. (d) Hoffmann, T.; Waibel, R.; Gmeiner, P. *J. Org. Chem.* **2003**, *68*, 62.
[195] For examples of olefin isomerization with metathesis catalysts, see (a) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390. (b) Lehman, S. E., Jr.; Schwendeman, J. E.; O'Donnell, P. M.; Wagener, K. B. *Inorg. Chim. Acta* **2003**, *345*, 190. (c) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414.
[196] Approximately 10-15% of enamide was usually observed under these conditions.

Table 1.12. *N*-Allylation and ring-closing metathesis for the formation of azaspirononanes from *C*,*C*-dicyclopropylmethylamides



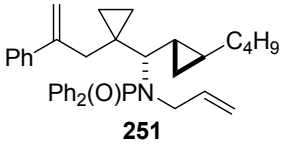
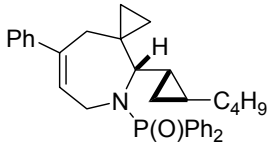
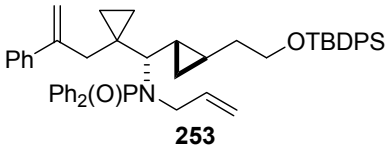
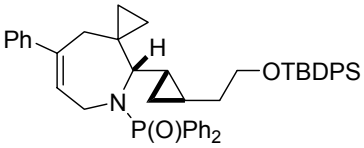
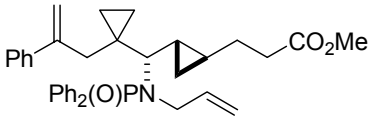
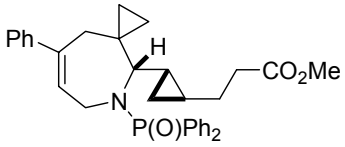
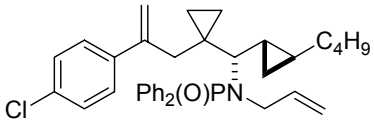
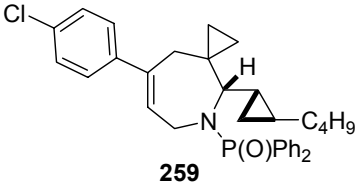
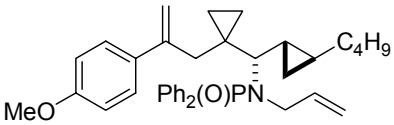
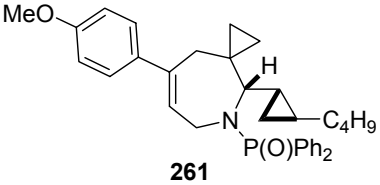
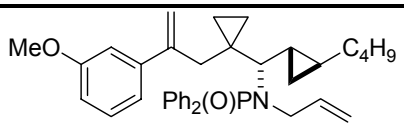
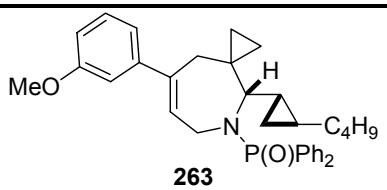
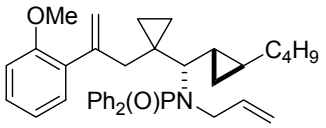
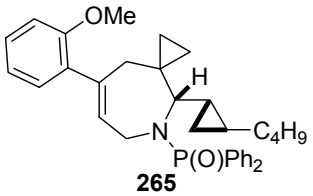
entry	amide	*N*-allylation product	yield (%)[a]	metathesis product	yield (%)[b]
1	**202**	 **251**	95	 **252**	75
2	**219**	 **253**	88	 **254**	71
3	**255**	 **256**	65	 **257**	55
4	**217**	 **258**	75	 **259**	72
5	**214**	 **260**	69	 **261**	80

Table 1.12. Cont'd

entry	amide	*N*-allylation product	yield (%)[a]	metathesis product	yield (%)[b]
6	**215**	 **262**	96	 **263**	75
7	**216**	 **264**	89	 **265**	84

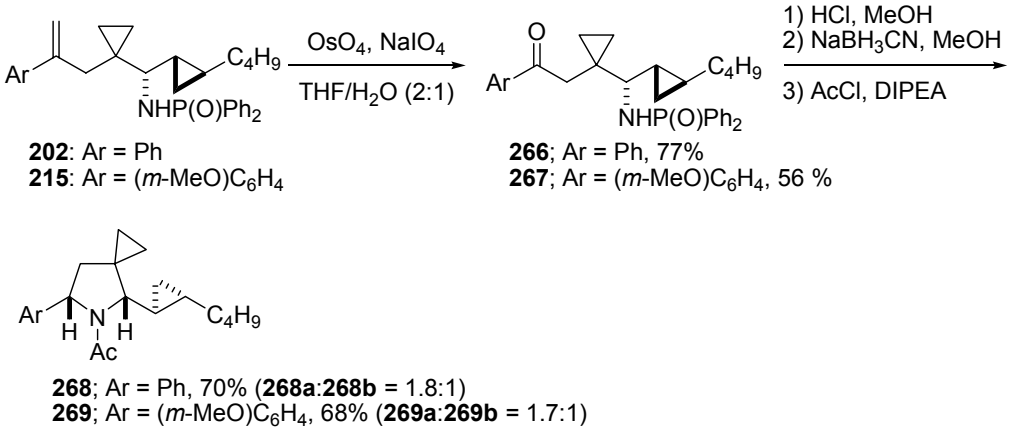
[a]Yield of isolated, analytically pure product based on phosphinamide; [b]Yield of isolated, analytically pure product based on allyl phosphinamide

Functionalization was tolerated both in the arene portion as well as the cyclopropane-containing side chain. Isomerization of the styrenyl olefin in **249** or **250** was never observed under these reaction conditions.[197]

The functionality present in the *C*,*C*-dicyclopropylmethylamide scaffold also affords the opportunity to prepare pyrrolidines by a reductive amination pathway (Scheme 1.30). Oxidative cleavage of the 1,1-disubstituted olefin in **202** and **215** using the protocol developed by Johnson and Lemieux afforded the aryl ketones **266** and **267** in good yields.[198] Unfortunately, direct reductive amination under Lewis acidic conditions (Ph_3SiH/BF_3•OEt_2,[199] $TiCl_4/Et_3SiH$) failed to afford the desired pyrrolidine.[200] We have previously taken advantage of the acid lability of the diphenylphosphinoyl group for derivatization and found that a simple three-step, one-pot protocol involving *N*-deprotection (HCl, MeOH) followed by reductive amination ($NaBH_3CN$, MeOH) and acylation (AcCl, DIPEA) could be used to generate the pyrrolidines **268** and **269**.

[197] Prolonged storage of these unsaturated azepines at r.t. leads to presumed isomerization to an enamide product, although this by-product has not been rigorously characterized.
[198] (a) Pappo, R.; Allen, D. S.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478. (b) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106.
[199] Rudolph, A. C.; Machauer, R.; Martin, S. F. *Tetrahedron Lett.* **2004**, *45*, 4895.
[200] The Lewis acidic conditions appear to promote the *N*-dephosphinoylation and the desired pyrrolidines could not be isolated in acceptable yields.

While the observed diastereoselection for pyrrolidine formation was poor (<2:1), the diastereomers were easily separated by column chromatography.[201]



202: Ar = Ph
215: Ar = (*m*-MeO)C_6H_4

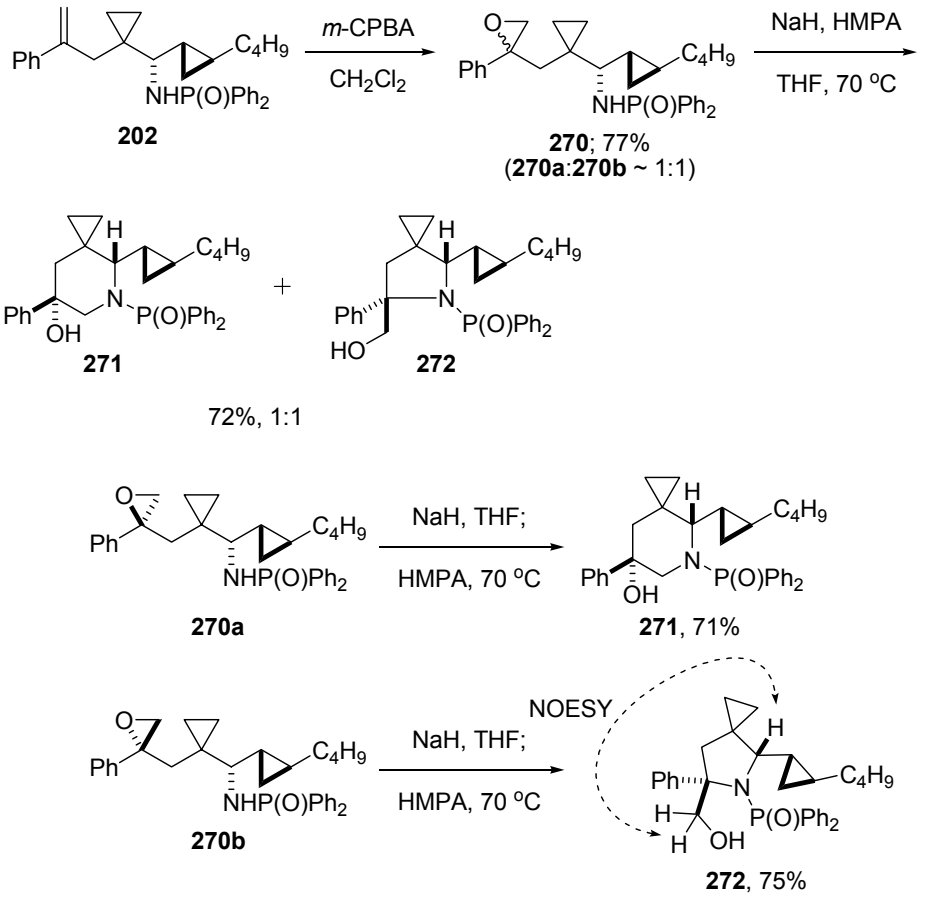
266; Ar = Ph, 77%
267; Ar = (*m*-MeO)C_6H_4, 56 %

268; Ar = Ph, 70% (**268a**:**268b** = 1.8:1)
269; Ar = (*m*-MeO)C_6H_4, 68% (**269a**:**269b** = 1.7:1)

Scheme 1.30. Reductive amination approach for the synthesis of azaspiroheptanes

Finally, we believed that the corresponding piperidine scaffold could be accessed using the intramolecular aminolysis of epoxide **270** (Scheme 1.31).[202] Not surprisingly, the epoxidation of **202** with *m*-CPBA was not influenced by the remote stereocenters affording a 1:1 mixture of diastereomeric epoxides **270a** and **270b**. The mixture was subjected to the conditions developed for the *N*-alkylation of phosphinamides **248** with allyl iodide. To our surprise, a stereodivergent pathway was revealed and two cyclization products, piperidine **271** and pyrrolidine **272** were isolated, each as single diastereomers. We surmised that the diastereomeric epoxides each afforded a single heterocyclic product. We were intrigued by the possibility of a stereospecific cyclization event and to test our conjecture, **270a** and **270b** were separated by column chromatography and individually reacted under our cyclization conditions. To our delight, **270a** afforded only piperidine **271** while **270b** afforded only pyrrolidine **272**. The relative stereochemistry of **272** was confirmed by the presence of a NOESY cross peak between the methine hydrogen and the hydroxymethylene group. The relative stereochemistry of **270a** and **270b** was inferred on the basis of an assumed inversion of stereochemistry for the conversion of **270b** to **272**.

[201] Similar results were observed by Martin and co-workers under these reductive amination conditions. They were able to improve the diastereoselectivity using the combination of $Ph_3SiH/BF_3{\bullet}OEt_2$.For details, see ref. 199.
[202] (a) LaLonde, R. T.; Muhammad, N.; Wong, C. F.; Sturiale, E. R. *J. Org. Chem.* **1980**, *45*, 3664. (b) Nuhrich, A.; Moulines, J. *Tetrahedron* **1991**, *47*, 3075. (c) Breternitz, H.-J.; Schaumann, E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1927. (d) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583.



Scheme 1.31. Stereospecific formation of azaspiroheptanes and azaspirooctanes by intramolecular epoxide aminolysis

At this stage, we can only speculate about the nature of this selective cyclization; however, it has been demonstrated that the cyclopropyl side chain plays an important role in this cyclization (Figure 1.11). When the cyclopropyl side chain is replaced with either R^2 = H or Me (R^1 = Ph),[203] only the 6-*endo* cyclization products are observed. The regioselectivity of epoxide opening is reversed when R^1,R^2 = H, and only the 5-*exo* product is formed.[203] With these control experiments in mind, it is reasonable to conclude that in the absence of a bulky substituent at R^2, the 6-*endo* mode of cyclization is favored for 1,1-disubstituted epoxides. However, as the size of R^2 increases, the preference for R^2 to remain pseudo-equatorial forces the reaction to the 5-*exo* cyclization pathway for **273b**. For epoxide **273a**, the interaction of the diphenylphosphinoyl

[203] These experiments were performed by Mr. Maciej Walczak. When R^2=Me, both diastereomers of the epoxide afford the 6-*endo* cyclization product.

group and R^1 must disfavor the conformer that would lead to the product of 5-*exo* opening, **274**. Rotation of R^2 away from the nitrogen protecting group to conformer **B** favors the 6-*endo* opening (in a boat-like transition state), leading to piperidine **275**. When R^2 is small, this preference must outweigh the A-value of the methyl group, forcing it axial in one diastereomer. Conversely, when R^2 is large, the ring flip to put R^2 axial is disfavored and the 5-*exo* pathway predominates affording pyrrolidine **276**.

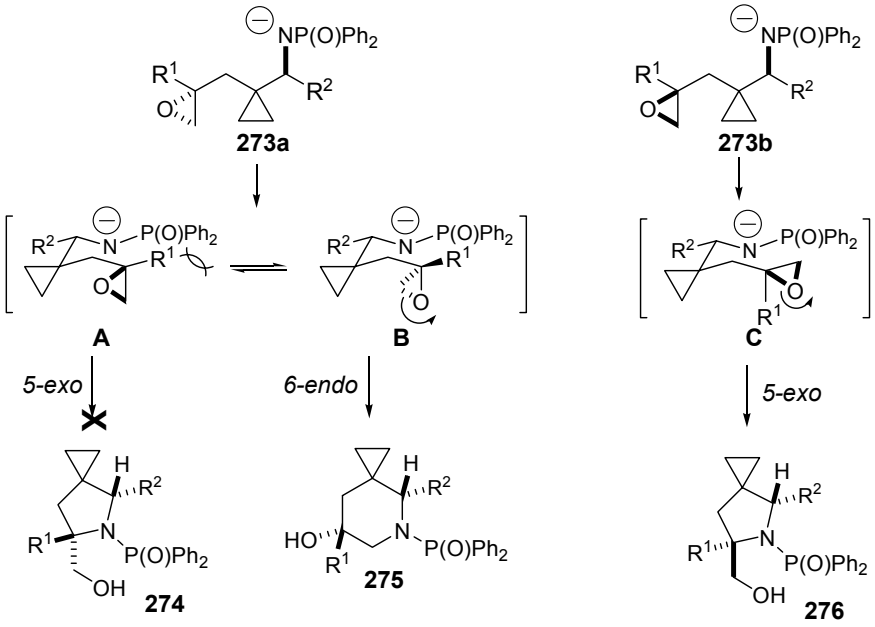


Figure 1.11. Predictive model for the stereospecificity of epoxide aminolysis

1.4 Microwave-Assisted Reactions of Alkenylzirconocenes[204]

The addition of alkenylzinc reagents to imines is a valuable protocol for the preparation of allylic- and *C*-cyclopropylalkylamides. The foremost disadvantage, in terms of library preparation, is the investment of time required from hydrozironcation until reaction completion (ca. 8-24 h). In the case of alkyne **231**, the addition to imine **201** was extremely slow (incomplete after 24 h) under our standard reaction conditions (Scheme 1.28). Using microwave irradiation, the addition of the vinylzinc reagent proceeded in only 30 min at 90 °C. Since the hydrozirconation of alkynes is prohibitively slow in toluene, this improved protocol still required a solvent switch from THF to toluene. Interestingly, the hydrozirconation was also found to be

[204] Wipf, P.; Janjic, J.; Stephenson, C. R. J. *Org. Biomol. Chem.* **2004**, *2*, 443.

significantly accelerated by microwave irradiation; the hydrozirconation of **108** in toluene is complete within 5 min at 60 °C.[205] Upon transmetalation to zinc, the addition of the vinylzinc reagent to **21** was complete after 5 min at 100 °C (Table 1.13). A simplified work-up protocol was also used for the rapid preparation of allylic amides (entries 1 and 2) employing a MeOH quench at 0 °C and filtration through a pad of SiO_2 prior to chromatography.[206] The unsymmetrical internal alkynes **231** and **279** were hydrozirconated in toluene under optimized conditions at 60 °C followed by addition to **21** and **119** at 100 °C in only 5 min (entries 3 and 4). This protocol has also been applied to the synthesis of *C*-cyclopropylalkylamides (entries 5-7), however the hydrozirconation of alkynes **281**, **108**, **125** was carried out in CH_2Cl_2 at r.t. Transmetalation to dimethylzinc at -78 °C, followed by addition to **21** or **119** in CH_2Cl_2 at 100 °C affords a mixture of allylic- and *C*-cyclopropylalkylamide. After cooling to 0 °C, CH_2I_2 is added and the reactions were further heated in the microwave for 20 min to complete the conversion of allylic amides to cyclopropanes **282**, **111** and **176** in good yields and excellent diastereoselectivity.[207]

In order to expand the diversity of compounds available using the microwave technology, the *C*-cyclopropylalkylamide **282** was *N*-deprotected in acidic methanol and the intermediate hydrochloride salt **283** was coupled with an acid chloride, a sulfonyl chloride and a chloroformate to afford the amide **284**, sulfonamide **285** and carbamate **286** in excellent yields over two steps (Scheme 1.32).[208]

---

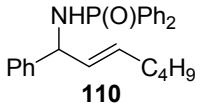
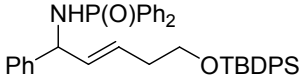
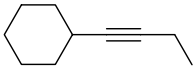
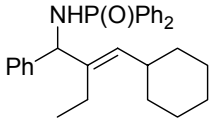
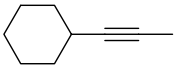
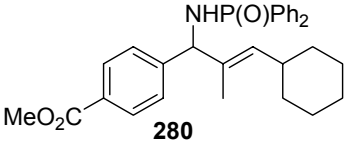
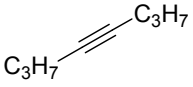
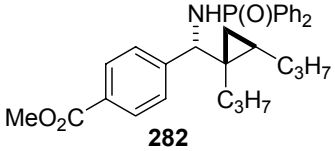
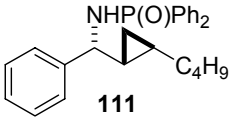
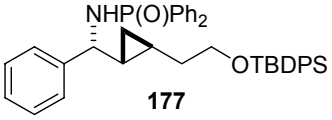
[205] Heating the hydrozirconation reaction also seems to accelerate a decomposition pathway, often leading to a purple coloration of the reaction. This color fades on cooling or addition of Me_2Zn and imine.

[206] This modification greatly simplifies the work-up protocol, avoiding emulsions often associated with the aqueous quench of the organometallic reaction.

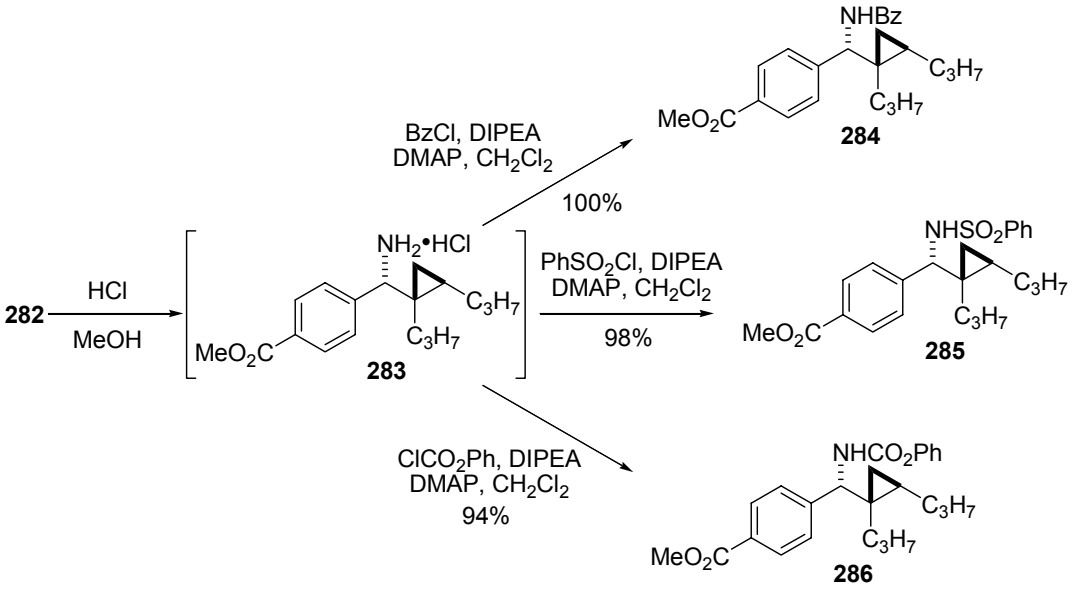
[207] The minor diastereomer was not observed in the ^1H NMR of the crude reaction mixture.

[208] The microwave protocols developed herein and analogous protocols developed for allylic amide derivatization by Jelena Janjic and Dr. Christopher Kendall have been adapted by the UPCMLD for the preparation of a library of allylic- and *C*-cyclopropylalkylamides. *Cf.* Wipf, P.; Coleman, C. M.; Janjic, J.; Iyer, P. S.; Fodor, M. D.; Shafer, Y. A.; Stephenson, C. R. J.; Kendall, C.; Day, B. W. *J. Comb. Chem.* **2005**, *In Press*.

Table 1.13. Microwave-accelerated synthesis of allylic- and *C*-cyclopropylalkylamides

entry	alkyne	imine	product	yield (%)[a]
1	**108**	**21**	 **110**	73
2	**125**	**21**	 **277**	62
3	 **231**	**21**	 **278**	63[b]
4	 **279**	**119**	 **280**	60[b]
5	 **281**	**119**	 **282**	61[c]
6	**106**	**21**	 **111**	61[c]
7	**125**	**21**	 **177**	68[c]

[a]Yield of isolated, analytically pure product based on imine; [b]Alkynes **231** and **279** were treated with 1.5 eq. Cp_2ZrHCl at 60 °C for 30 min; [c]Hydrozirconation in CH_2Cl_2 at r.t.



Scheme 1.32. Diversification of the *C*-cyclopropylalkylamide scaffold

1.5 Conclusions

In summary, a number of efficient protocols have been developed for the preparation of a diverse assortment of products which would have been previously available only using multi-step protocols (Figure 1.12). The preparation of simple allylic amines and alcohols has been described using a straightforward, one-pot protocol. This method has been extended to the synthesis of *C*-cyclopropylalkylamides, hinging only upon the choice of solvent for the reaction. Furthermore, the use of functionalized imines has led to the discovery of a novel cascade reaction for the preparation of *C*,*C*-dicyclopropylmethylamides from simple, readily available starting materials. Highlights of this cascade are the formation of ten new carbon-carbon bonds, the scission of an *sp*-*sp* bond and the diastereocontrolled construction of three new stereocenters. Products of these reactions have been used in a diversity-oriented approach for the preparation of 7-, 8-, and 9-membered azaspirocyclic ring structures based on reductive amination, epoxide opening or ring-closing metathesis strategies.

From the simple allylic amines and alcohols **288**, **289**, and **289** to more complex heterocyclic scaffolds, such as azaspirocycles **294**-**297**, the practical protocols for the preparation of these building blocks should prove useful for the preparation of libraries for the discovery and evaluation of novel lead structures for biological evaluation. The highlight of the reactions described in Chapter 1 is the remarkable cooperativity of zirconium and zinc and it is expected that the interplay of these metals will continue to provide opportunities for new reaction discovery.

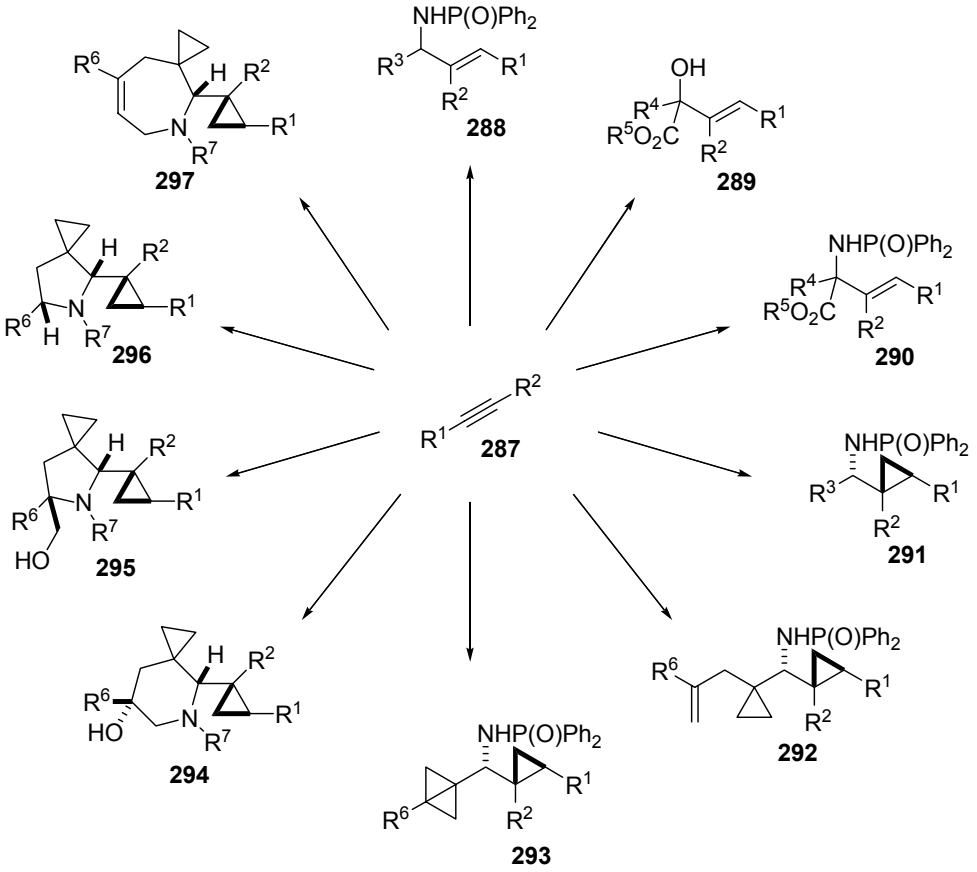


Figure 1.12. Summary of oxygen- and nitrogen-containing products that have been prepared using the Zr→Zn transmetalation addition pathway

1.6 Experimental Part

General. All moisture-sensitive reactions were performed under an atmosphere of N_2 and glassware was flame dried under vacuum or dried in an oven at 140 °C for 2 h prior to use. DME and Et_2O and THF were dried by distillation over Na/Benzophenone and Et_3N, *i*-Pr_2NH and $Cl(CH_2)_2Cl$ were dried by distillation over CaH_2. Toluene and CH_2Cl_2 were purified by filtration through activated alumina. CD_2Cl_2 was used from a freshly opened ampule without purification. Me_3Al (neat), Me_2Zn (2.0 M in toluene), Et_2Zn (neat), and CH_2I_2 were purchased from the Aldrich Chemical Company. Unless otherwise stated, solvents or reagents were used as received. Cp_2ZrHCl,[209] **118**,[210] imines **21**,[210] **119**,[210] **123**,[210] **124**,[210] alkynes **125**,[211] **127**,[212] **141**,[213] **178**,[214] **223**,[215] **231**,[216] **279**[217] and allylic amide **228**[215] were prepared according to literature procedures. $Zn(CH_2I)_2$ was prepared by dropwise addition of CH_2I_2 (0.20 mL, 2.4 mmol) to a freshly prepared solution of Et_2Zn (0.15 g, 1.2 mmol) in $Cl(CH_2)_2Cl$ (1.0 mL) at –20 °C and stirring for 10 min. $Zn(CH_2I)_2$•DME was prepared by dropwise addition of CH_2I_2 (0.59 mL, 7.3 mmol) to a freshly prepared solution of Et_2Zn (0.45 g, 3.6 mmol) and DME (0.39 mL, 3.6 mmol) in $Cl(CH_2)_2Cl$ (3.0 mL) at –30 °C and and used after stirring for 10 min.

Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F-254 plates (particle size 0.040-0.055 mm, 230-400 mesh) and visualization was accomplished with a 254 nm UV light and/or by staining with Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}$•$4H_2O$ and 0.20 g of $Ce(SO_4)_2$ in 100 mL of 3.5 N H_2SO_4 solution) or $KMnO_4$ (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% aqueous NaOH solution).

Unless stated otherwise, NMR spectra were recorded at 300 MHz/76 MHz (^{1}H NMR/^{13}C NMR) using a Bruker AVANCE 300 MHz spectrometer at 21 °C in $CDCl_3$. High field 500 MHz/126 MHz (^{1}H NMR/^{13}C NMR) and 600 MHz/151 MHz (^{1}H NMR/^{13}C NMR) were recorded on Bruker AVANCE 500 MHz and 600 MHz spectrometers respectively. Chemical

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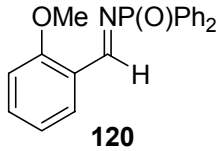
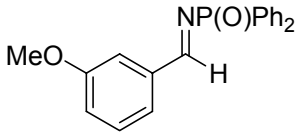
shifts (δ) are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broad), coupling constants, and integration. For all phosphorous containing compounds, data for ^{13}C spectra are tabulated by observed peak. IR spectra were obtained on a Nicolet AVATAR 360 FT-IR E.S.P. spectrometer. Mass spectra were obtained on a Micromass Autospec double focusing instrument. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Microwave experiments were run on a CEM Discover instrument or a Personal Chemistry workstation.



120

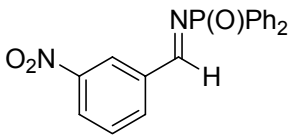
***N*-(2-Methoxybenzylidene)-*P*,*P*-diphenylphosphinamide** (**120**). According to a literature procedure,[210] **118** (1.0 g, 4.6 mmol), *o*-anisaldehyde (0.63 g, 4.6 mmol), $TiCl_4$ (0.30 mL, 2.8 mmol), and Et_3N (1.9 mL, 14 mmol) in CH_2Cl_2 (24 mL) afforded **120** (0.82 g, 53%) as a colorless solid: mp 142.0-144.0 °C (hexanes/EtOAc); IR (KBr) 3052, 3018, 2966, 2942, 2840, 1681, 1608, 1597, 1576, 1487, 1468, 1638, 1365, 1302, 1290, 1249, 1204, 1179, 1162, 1122 cm^{-1}; ^1H NMR δ 9.81 (d, *J* = 32.6 Hz, 1 H), 8.24 (dd, *J* = 7.8, 1.7 Hz, 1 H), 7.99-7.92 (m, 4 H), 7.56-7.42 (m, 7 H), 7.05 (t, *J* = 7.4 Hz, 1 H), 6.96 (d, *J* = 8.4 Hz, 1 H), 3.89 (s, 3 H); ^{13}C NMR δ 170.15, 170.06, 161.32, 132.05, 131.83, 131.79, 131.75, 131.71, 128.65, 128.48, 128.33, 120.76, 111.61, 55.68; MS (EI) *m/z* (intensity) 335 (M^+, 16), 304 (36), 216 (34), 202 (100), 155 (21), 134 (67), 77 (50); HRMS (EI) *m/z* calculated for $C_{20}H_{18}NO_2P$ 335.1075, found 335.1083.



121

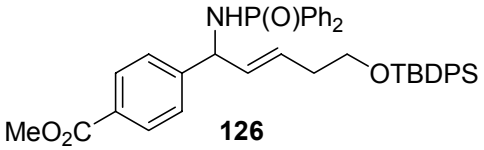
***N*-(3-Methoxy-benzylidene)-*P*,*P*-diphenylphosphinamide** (**121**). According to a literature procedure,[210] **118** (1.0 g, 4.6 mmol), *m*-anisaldehyde (0.63 g, 4.6 mmol), $TiCl_4$ (0.30 mL, 2.8 mmol), and Et_3N (1.9 mL, 14 mmol) in CH_2Cl_2 (24 mL) afforded **121** (0.45 g, 29%) as a colorless solid: mp 89.5-92.0 °C (hexanes/EtOAc); IR (KBr) 3080, 3057, 2946, 2845, 1685, 1615, 1579, 1491, 1436, 1275, 1204, 1156, 1128, 1109 cm^{-1}; ^1H NMR δ 9.29 (d, *J* = 31.9 Hz, 1 H), 7.98-7.91 (m, 4 H), 7.59-7.40 (m, 9 H), 7.16-7.15 (m, 1 H), 3.90 (s, 3 H); ^{13}C NMR δ 173.59, 173.49, 160.04, 137.37, 137.04, 133.89, 132.21, 131.67, 131.54, 131.42, 129.86, 128.44, 128.28,

123.35, 119.85, 113.78, 55.31; MS (EI) *m/z* (intensity) 335 (M^+, 11), 216 (100), 199 (81), 140 (48), 124 (60), 77 (62); HRMS (EI) *m/z* calculated for $C_{20}H_{18}NO_2P$ 335.1075, found 335.1082.



122

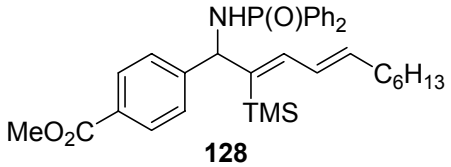
***N*-(3-Nitro-benzylidene)-*P*,*P*-diphenylphosphinamide** (**122**). According to a literature procedure,[210] **118** (1.0 g, 4.6 mmol), *m*-nitrobenzaldehyde (0.70 g, 4.6 mmol), $TiCl_4$ (0.30 mL, 2.8 mmol), and Et_3N (1.9 mL, 14 mmol) in CH_2Cl_2 (24 mL) afforded **122** (0.36 g, 22%) as a light yellow solid: IR (KBr) 3074, 1652, 1623, 1574, 1529, 1438, 1350, 1211, 1185, 1125, 1109 cm^{-1}; ^1H NMR δ 9.41 (d, *J* = 31.0 Hz, 1 H), 8.90 (s, 1 H), 8.46-8.43 (m, 1 H), 8.27 (d, *J* = 7.7 Hz, 1 H), 8.00-7.93 (m, 4 H), 7.73 (t, *J* = 7.8 Hz, 1 H), 7.58-7.47 (m, 6 H); ^{13}C NMR δ 171.30, 171.20, 137.57, 137.23, 136.37, 133.08, 132.40, 132.37, 132.08, 131.94, 131.84, 131.72, 131.39, 130.39, 128.95, 128.78, 128.63, 127.79, 123.95; MS (EI) *m/z* (intensity) 350 (M^+, 10), 201 (100), 77 (17); HRMS (EI) *m/z* calculated for $C_{19}H_{15}N_2O_3P$ 350.0820, found 350.0809.



126

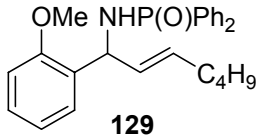
Methyl 4-[1-(diphenylphosphinoyl)amino-5-(*tert*-butyldiphenylsilanyloxy)pent-2-enyl]-benzoate (**126**). **General Protocol A**. To a suspension of Cp_2ZrHCl (0.11g, 0.41 mmol) in dry CH_2Cl_2 (1.0 mL) was added a solution of **125** (0.13 g, 0.41 mmol) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred for 5 min and all volatile material was removed in vacuo. The residue was dissolved in dry toluene (2.0 mL), cooled to -78 °C, treated with Me_2Zn (0.21 mL, 0.41 mmol, 2.0 M in toluene), warmed to 0 °C and treated with **119** (0.10 g, 0.28 mmol). The reaction mixture was warmed to r.t., stirred for 1.5 h, quenched with sat. NH_4Cl, diluted with EtOAc and filtered through Celite. The mixture was extracted with EtOAc (3x) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (1:4, hexanes/EtOAc containing 1% v/v Et_3N) to give **126** (0.15 g, 82%) as a colorless foam: IR (neat) 3175, 3171, 2953, 2931, 2857, 1722, 1438, 1281, 1189, 1111 cm^{-1}; ^1H NMR δ 7.97-7.90 (m, 4 H), 7.83-7.75 (m, 2 H), 7.64-7.60 (m, 4 H), 7.51-7.33 (m, 14 H), 5.77-5.69 (m, 1 H), 5.56-5.46 (m 1 H), 4.88-4.80 (m, 1 H), 3.92

(s, 3 H), 3.63 (t, *J* = 6.5 Hz, 2 H), 3.28 (dd, *J* = 9.8, 6.2 Hz, 1 H), 2.27 (q, *J* = 6.6 Hz, 2 H), 1.00 (s, 9 H); ^{13}C NMR δ 167.01, 147.93, 147.87, 135.66, 133.91, 133.42, 133.30, 133.23, 132.43, 132.34, 132.30, 132.21, 132.11, 132.08, 132.05, 132.01, 131.71, 131.51, 129.97, 129.76, 129.71, 129.15, 128.68, 128.64, 128.51, 128.47, 127.77, 127.26, 63.35, 56.63, 52.23, 35.67, 26.95, 19.32; MS (EI) *m/z* (intensity) 616 ([M-C_4H_9]$^+$, 3), 467 (3), 437 (5), 379 (8), 309 (86), 199 (100), 183 (36), 135 (31), 111 (61), 83 (77), 69 (86); HRMS (EI) *m/z* calculated for $C_{37}H_{35}NO_4SiP$ (M-C_4H_9) 616.2073, found 616.2087.



128

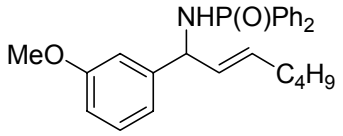
Methyl 4-[1-(diphenylphospinoyl)amino-2-(trimethylsilanyl)undeca-2,4-dienyl]benzoate (**128**). According to the General Protocol A, Cp_2ZrHCl (0.15 g, 0.58 mmol), **127** (0.12 g, 0.58 mmol), Me_2Zn (0.29 mL, 0.58 mmol, 2.0 M in toluene) and **119** (0.14 g, 0.38 mmol) (14 h reaction time) afforded **128** (0.12 g, 52%) as a light yellow solid: mp 136.0-138.0 °C (hexanes/EtOAc); IR (KBr) 3114, 2953, 2927, 2857, 1722, 1609, 1437, 1278, 1193, 1107 cm^{-1}; ^{1}H NMR δ 7.96-7.83 (m, 6 H), 7.49-7.38 (m, 8 H), 6.86 (d, *J* = 11.2 Hz, 1 H), 6.47-6.38 (m, 1 H), 5.87-5.78 (m, 1 H), 4.99 (t, *J* = 10.9 Hz, 1 H), 3.88 (s, 3 H), 3.28 (dd, *J* = 10.2, 6.3 Hz, 1 H), 2.22-2.16 (m, 2 H), 1.49-1.42 (m 2 H), 1.40-1.24 (bm, 6 H), 0.93-0.89 (m, 3 H), 0.07 (s, 9 H); ^{13}C NMR δ 167.11, 148.58, 148.54, 142.13, 140.40, 140.35, 138.65, 133.79, 132.92, 132.79, 132.15, 132.10, 132.02, 131.17, 129.97, 129.16, 128.75, 128.59, 128.45, 128.23, 59.90, 52.24, 33.05, 31.89, 29.20, 29.07, 22.85, 14.30, 0.44; MS (EI) *m/z* (intensity) 573 (M$^+$, 2), 558 (11), 364 (6), 323 (19), 274 (10), 201 (14), 181 (27), 73 (100); HRMS (EI) *m/z* calculated for $C_{33}H_{41}NO_3PSi$ (M-CH_3) 558.2593, found 558.2573.



129

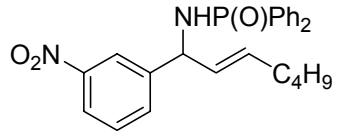
***N*-[1-(2-Methoxyphenyl)-hept-2-enyl]-*P*,*P*-diphenylphosphinamide** (**129**). According to the General Protocol A, Cp_2ZrHCl (0.12 g, 0.45 mmol), **108** (51 μL, 0.48 mmol), Me_2Zn (0.22 mL, 0.45 mmol, 2.0 M in toluene) and **120** (0.10 g, 0.30 mmol) (1 h reaction time) afforded **129** (0.10 g, 80%) as a colorless solid: mp 126.0-127.5 °C (hexanes/EtOAc); IR (KBr) 3433, 3174,

2918, 1597, 1492, 1436, 1241, 1184 cm^{-1}; ^1H NMR δ 7.92-7.76 (m, 4 H), 7.49-7.33 (m, 6 H), 7.27-7.21 (m, 1 H), 7.06 (dd, *J* = 7.5, 1.7 Hz, 1 H), 6.92-6.84 (m, 2 H), 5.77 (ddt, *J* = 15.3, 6.3, 1.3 Hz, 1 H), 5.42 (dtd, *J* = 15.1, 6.7, 1.4 Hz, 1 H), 4.86 (dt, *J* = 9.9, 5.9 Hz, 1 H), 4.10 (dd, *J* = 10.5, 8.0 Hz, 1 H), 3.74 (s, 3 H), 1.97-1.93 (m, 2 H), 1.29-1.25 (m, 4 H), 0.88-0.83 (m, 3 H); ^{13}C NMR δ 156.85, 134.35, 133.64, 132.64, 132.54, 132.35, 132.16, 131.92, 131.75, 131.71, 131.64, 131.61, 131.25, 131.18, 128.52, 128.44, 128.40, 128.35, 128.22, 120.93, 111.25, 55.37, 54.80, 31.93, 31.40, 22.30, 14.07; MS (EI) *m/z* (intensity) 419 (M^+, 10), 362 (19), 336 (8), 218 (100), 201 (50), 118 (8), 91 (11), 77 (15); HRMS (EI) *m/z* calculated for $C_{26}H_{30}NO_2P$ 419.2014, found 419.2012.



130

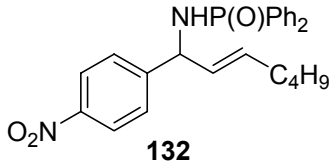
***N*-[1-(3-Methoxy-phenyl)-hept-2-enyl]-*P*,*P*-diphenylphosphinamide** (**130**). According to the General Protocol A, Cp_2ZrHCl (0.12 g, 0.45 mmol), **108** (51 μL, 0.45 mmol), Me_2Zn (0.22 mL, 0.45 mmol, 2.0 M in toluene) and **121** (0.10 g, 0.30 mmol) (4 h reaction time) afforded **130** (83 mg, 66%) as a colorless solid: mp 74.0-77.2 °C (hexanes/EtOAc); IR (KBr) 3189, 3056, 2953, 2930, 2869, 1599, 1489, 1463, 1437, 1257, 1184, 1122, 1109 cm^{-1}; ^1H NMR δ 7.98-7.84 (m, 4 H), 7.56-7.39 (m, 6 H), 7.31-7.21 (m, 1 H), 6.99-6.90 (m, 2 H), 6.82 (dd, *J* = 8.2, 2.4 Hz, 1 H), 5.68 (dd, *J* = 15.3, 6.0 Hz, 1 H), 5.61-5.51 (m, 1 H), 4.85-4.77 (m, 1 H), 3.82 (s, 3 H), 3.33 (dd, *J* = 9.2, 6.4 Hz, 1 H), 2.05-1.99 (m, 2 H), 1.34-1.28 (m, 4 H), 0.94-0.89 (m, 3 H); ^{13}C NMR δ 159.83, 144.97, 144.89, 133.93, 133.58, 132.74, 132.53, 132.49, 132.45, 132.40, 132.32, 132.22, 132.00, 131.95, 131.91, 131.87, 131.73, 131.67, 119.46, 112.92, 112.73, 57.11, 55.39, 32.01, 31.35, 22.45, 14.13; MS (EI) *m/z* (intensity) 419 (M^+, 10), 362 (5), 336 (5), 218 (100), 201 (47), 77 (42); HRMS (EI) *m/z* calculated for $C_{26}H_{30}NO_2P$ 419.2014, found 419.2023.



131

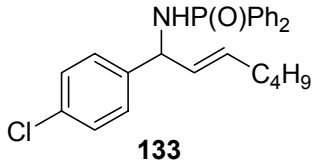
***N*-[1-(3-Nitrophenyl)hept-2-enyl]-*P*,*P*-diphenylphosphinamide** (**131**). According to the General Protocol A, Cp_2ZrHCl (0.11 g, 0.43 mmol), **108** (49 μL, 0.43 mmol), Me_2Zn (0.21 mL, 0.43 mmol, 2.0 M in toluene) and **122** (0.10 g, 0.28 mmol) (1.5 h reaction time) afforded **131**

(93 mg, 75%) as a light yellow solid: mp 120.0-121.5 °C (hexanes/EtOAc); IR (KBr) 3177, 3060, 2955, 2931, 2858, 1526, 1453, 1436, 1350, 1182, 1141, 1124 cm^{-1}; ^1H NMR δ 8.15-8.13 (m, 1 H), 8.04-8.01 (m, 1 H), 7.93-7.86 (m 2 H), 7.79-7.68 (m 3 H), 7.53-7.39 (m, 5 H), 7.35-7.29 (m, 2 H), 5.65 (dd, *J* = 15.3, 6.4 Hz, 1 H), 5.53 (dt, *J* = 15.5, 6.3 Hz, 1 H), 4.88 (ddd, *J* = 9.7, 9.7, 6.4 Hz, 1 H), 3.69 (dd, *J* = 9.3, 6.9 Hz, 1 H), 2.04-1.97 (m, 2 H), 1.36-1.20 (m, 4 H), 0.89-0.84 (m, 3 H); ^{13}C NMR δ 148.30, 145.42, 145.36, 133.97, 133.84, 133.27, 133.18, 132.44, 132.31, 132.15, 132.03, 131.57, 131.47, 130.66, 130.58, 129.50, 128.72, 128.61, 128.55, 128.44, 122.26, 122.11, 56.40, 31.97, 31.20, 22.35, 14.02; MS (EI) *m/z* (intensity) 434 (M^+, 21), 417 (65), 377 (12), 233 (28), 218 (23), 201 (100), 77 (21); HRMS (EI) *m/z* calculated for $C_{25}H_{27}N_2O_3P$ 434.1759, found 434.1766.



132

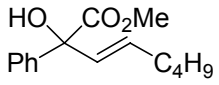
***N*-[1-(4-Nitrophenyl)hept-2-enyl]-*P*,*P*-diphenylphosphinamide** (**132**). According to the General Protocol A, Cp_2ZrHCl (0.11 g, 0.43 mmol), **108** (49 μL, 0.43 mmol), Me_2Zn (0.21 mL, 0.43 mmol, 2.0 M in toluene) and **123** (0.10 g, 0.28 mmol) (1 h reaction time) afforded **132** (90 mg, 73%) as a light yellow solid: mp 138.5-141.0 °C (hexanes/EtOAc); IR (KBr) 3153, 2958, 2928, 2970, 1606, 1595, 1519, 1438, 1345, 1182, 1123, 1111 cm^{-1}; ^1H NMR δ 8.14 (d, *J* = 8.6 Hz, 2 H), 7.95-7.88 (m, 2 H), 7.82-7.76 (m, 2 H), 7.56-7.44 (m, 6 H), 7.40-7.34 (m, 2 H), 5.64 (dd, *J* = 15.4, 6.1 Hz, 1 H), 5.57-4.48 (m, 1 H), 4.90 (dt, *J* = 9.8, 6.4 Hz, 1 H), 3.39 (dd, *J* = 9.4, 6.5 Hz, 1 H), 2.05-1.99 (m, 2 H), 1.36-1.22 (m, 4 H), 0.91-0.86 (m, 3 H); ^{13}C NMR δ 150.57, 150.52, 147.10, 134.13, 133.25, 133.08, 132.50, 132.37, 132.26, 132.22, 132.17, 132.13, 132.05, 131.54, 130.46, 128.77, 128.70, 128.60, 128.53, 128.18, 123.81, 56.57, 32.01, 31.22, 22.38, 14.06; MS (EI) *m/z* (intensity) 434 (M^+, 17), 377 (12), 233 (100), 201 (97), 155 (10), 77 (28); HRMS (EI) *m/z* calculated for $C_{25}H_{27}N_2O_3P$ 434.1759, found 434.1752.



133

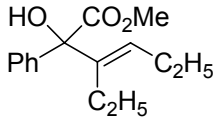
***N*-[1-(4-Chlorophenyl)hept-2-enyl]-*P*,*P*-diphenylphosphinamide** (**133**). According to the General Protocol A, Cp_2ZrHCl (0.11 g, 0.44 mmol), **108** (51 μL, 0.44 mmol), Me_2Zn (0.22 mL,

0.441 mmol, 2.0 M in toluene) and **124** (0.10 g, 0.294 mmol) (2 h reaction time) afforded **133** (96 mg, 77%) as a light yellow solid: mp 147.4-149.2 °C (hexanes/EtOAc); IR (KBr) 3117, 3053, 2953, 2924, 2869, 1491, 1456, 1437, 1194, 1181, 1171, 1121, 1109 cm^{-1}; ^1H NMR δ 7.96-7.90 (m, 2 H), 7.85-7.78 (m, 2 H), 7.55-7.36 (m, 6 H), 7.37-7.24 (m, 4 H), 5.64 (dd, *J* = 15.3, 6.0 Hz, 1 H), 5.55-4.46 (m, 1 H), 4.79 (dt, *J* = 9.7, 6.2 Hz, 1 H), 3.24 (dd, *J* = 9.4, 6.1 Hz, 1 H), 2.04-1.97 (m, 2 H), 1.32-1.28 (m, 4 H), 0.91-0.87 (m, 3 H); ^{13}C NMR δ 141.75, 141.69, 133.59, 133.47, 133.10, 133.03, 132.51, 132.38, 132.32, 132.19, 132.06, 132.02, 131.00, 131.96, 131.88, 131.77, 131.44, 131.38, 128.72, 128.66, 128.50, 128.48, 56.42, 31.99, 31.32, 22.41, 14.10; MS (EI) *m/z* (intensity) 423 (M^+, 8), 222 (87), 201 (100), 125 (26), 115 (19), 77 (64); HRMS (EI) *m/z* calculated for $C_{25}H_{27}NOPCl$ 423.1519, found 423.1523.



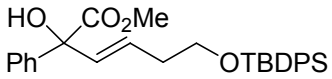
135

(*E*)-2-Hydroxy-2-phenyloct-3-enoic acid methyl ester (**135**). **General Protocol B**. To a suspension of Cp_2ZrHCl (0.24 g, 0.91 mmol) in dry CH_2Cl_2 (4.0 mL) was added **108** (0.10 mL, 0.91 mmol) and the reaction mixture was stirred for 10 min at r.t. The solvent was removed in vacuo, and the residue was dissolved in dry toluene (4.0 mL), cooled to -78 °C, treated with Me_2Zn (0.46 mL, 0.91 mmol, 2.0 M in toluene) and warmed to 0 °C. After addition of **134** (87 μL, 0.61 mmol) the reaction warmed to r.t. and stirred for 2 h, quenched with sat. NH_4Cl, diluted with EtOAc, and filtered through Celite. The layers were separated and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (19:1, hexanes/EtOAc) to give **135** (0.14 g, 93%) as a colorless oil: IR (neat) 3511, 3028, 3956, 2928, 2872, 2857, 1732, 1494, 1449, 1436, 1254, 1152 cm^{-1}; ^1H NMR δ 7.53-7.50 (m, 2 H), 7.39-7.30 (m, 3 H), 6.01-5.99 (m, 2 H), 3.80 (s, 3 H), 2.17-2.10 (m, 2 H), 1.44-1.30 (m, 4 H), 0.91 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR δ 175.26, 141.85, 132.61, 129.71, 128.39, 128.09, 126.34, 78.32, 53.53, 32.04, 31.31, 22.42, 14.08; MS (EI) *m/z* (intensity) 248 (M^+, 1), 189 (100), 133 (72), 105 (55), 91 (30); HRMS (EI) *m/z* calculated for $C_{15}H_{18}O_2$ (M-H_2O) 230.1307, found 230.1311.



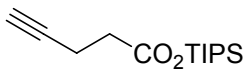
137

(*E*)-3-Ethyl-2-hydroxy-2-phenylhex-3-enoic acid methyl ester (**137**). According to the General Protocol B, Cp_2ZrHCl (0.24 g, 0.91 mmol), **136** (0.10 mL, 0.91 mmol), Me_2Zn (0.46 mL, 0.91 mmol, 2.0 M in toluene) and **134** (87 μL, 0.61 mmol) afforded **137** (0.11 g, 76%) as a colorless oil: IR (neat) 3503, 2965, 2935, 2874, 1728, 1493, 1449, 1436, 1375, 1249, 1170 cm^{-1}; ^1H NMR δ 7.56-7.53 (m, 2 H), 7.35-7.30 (m, 3 H), 5.26 (t, *J* = 7.2 Hz, 1 H), 3.82 (s, 3 H), 3.72 (bs, 1 H), 2.19-2.07 (m, 4 H), 0.99 (t, *J* = 7.5 Hz, 6 H); ^{13}C NMR δ 175.50, 141.36, 140.42, 131.78, 128.03, 127.78, 127.53, 83.59, 53.28, 22.03, 21.49, 15.04, 14.19; MS (EI) *m/z* (intensity) 248 (M^+, 0.1), 189 (60), 105 (49); HRMS (EI) *m/z* calculated for $C_{15}H_{20}O_3$ 248.1412, found 248.1410.



138

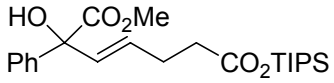
(*E*)-6-(*tert*-Butyldiphenylsilanyloxy)-2-hydroxy-2-phenylhex-3-enoic acid methyl ester (**138**). According to the General Protocol B, Cp_2ZrHCl (0.24 g, 0.91 mmol), **125** (0.28 g, 0.91 mmol), Me_2Zn (0.46 mL, 0.91 mmol, 2.0 M in toluene) and **134** (87 μL, 0.61 mmol) afforded **138** (0.24 g, 83%) as a colorless oil: IR (neat) 3510, 3070, 2954, 2931, 2857, 1734, 1489, 1472, 1447, 1428, 1256, 1149, 1112 cm^{-1}; ^1H NMR δ 7.69-7.66 (m, 4H), 7.54-7.51 (m, 2 H), 7.44-7.30 (m, 9 H), 6.13-5.99 (m, 2 H), 3.83-3.73 (m, 2 H), 3.78 (s, 3 H), 2.42, 2.38 (AB, *J* = 6.1 Hz, 2 H), 1.05 (s, 9 H); ^{13}C NMR δ 175.10, 141.65, 135.74, 133.94, 131.70, 129.76, 129.16, 128.48, 128.11, 127.81, 126.35, 78.32, 63.33, 53.54, 35.73, 26.98, 19.35; MS (EI) *m/z* (intensity) 456 ($[M-H_2O]^+$, 2), 399 (10), 355 (12), 199 (100), 169 (43), 135 (25), 105 (23), 91 (16); HRMS (EI) *m/z* calculated for $C_{29}H_{32}O_3Si$ (M-H_2O) 456.2121, found 456.2132.



139

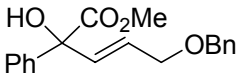
***O*-Triisopropylsilyl pent-4-ynoate (139)**. To a cooled (0 °C) solution of 4-pentynoic acid (1.1 g, 12 mmol) in dry CH_2Cl_2 (25 mL) was added imidazole (0.78 g, 12 mmol) and TIPS-Cl (2.2 g, 12 mmol) and the reaction was stirred for 2 h, diluted with CH_2Cl_2 and filtered through Celite. The solution was washed with H_2O, 10% HCl and brine, dried ($MgSO_4$) and concentrated. The

residue was purified by Kugelrohr distillation (90-120 °C @ ~1 mm Hg) to afford **139** (2.8 g, 94%) as a colorless oil: IR (neat) 3314, 2946, 2869, 1720, 1466, 1371, 1268, 1192 cm^{-1}; ^1H NMR δ 2.63-2.58 (m, 2 H), 2.53-2.48 (m, 2 H), 1.97 (t, *J* = 2.6 Hz, 1 H), 1.37-1.24 (m, 3 H), 1.09 (d, *J* = 7.2 Hz, 18 H); ^{13}C NMR δ 171.62, 82.67, 68.88, 34.84, 17.68, 14.63, 11.82; MS (EI) *m/z* (intensity) 254 (M^+, 0.1), 135 (25), 83 (100); HRMS (EI) *m/z* calculated for $C_{11}H_{19}O_2Si$ (M-C_3H_7) 211.1154, found 211.1146.



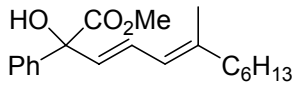
140

(*E*)-2-Hydroxy-2-phenylhept-3-enedioic acid 7-triisopropylsilyl ester 1-methyl ester (**140**). According to the General Protocol B, Cp_2ZrHCl (0.24 g, 0.91 mmol), **139** (0.23 g, 0.91 mmol), Me_2Zn (0.46 mL, 0.91 mmol, 2.0 M in toluene) and **134** (87 μL, 0.61 mmol) afforded **140** (0.21 g, 82%) as a colorless oil: IR (neat) 3507, 2947, 2868, 1720, 1465, 1449, 1436, 1369, 1256, 1187, 1140 cm^{-1}; ^1H NMR δ 7.52-7.49 (m, 2 H), 7.38-7.30 (m, 3 H), 6.12-5.97 (m, 2 H), 3.84-3.78 (m, 1 H), 3.80 (s, 3 H), 2.53-2.46 (m, 4 H), 1.37-1.22 (m, 3 H), 1.07 (d, *J* = 7.1 Hz, 18 H); ^{13}C NMR δ 174.93, 172.77, 141.85, 131.28, 130.42, 128.44, 128.06, 126.28, 78.33, 53.35, 35.41, 27.81, 17.92, 12.17; MS (EI) *m/z* (intensity) 402 ($[M-H_2O]^+$, 4), 359 (10), 345 (13), 283 (10), 187 (46), 121 (100), 105 (56); HRMS (EI) *m/z* calculated for $C_{23}H_{34}O_4Si$ (M-H_2O) 402.2226, found 402.2215.



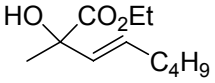
142

(*E*)-5-Benzyloxy-2-hydroxy-2-phenylpent-3-enoic acid methyl ester (**142**). According to the General Protocol B, Cp_2ZrHCl (0.52 g, 2.0 mmol), **141** (0.29 g, 2.0 mmol), Me_2Zn (1.0 mL, 2.0 mmol, 2.0 M in toluene) and **134** (0.19 mL, 1.3 mmol) afforded **142** (0.38 g, 90%) as a colorless oil: IR (neat) 3500, 3062, 3030, 2952, 2853, 1733, 1495, 1450, 1436, 1362, 1252 cm^{-1}; ^1H NMR δ 7.55-7.51 (m, 2 H), 7.38-7.34 (m, 8 H), 6.34 (dt, *J* = 15.4, 1.5 Hz, 1 H), 6.16 (dt, *J* = 15.4, 5.2 Hz, 1 H), 4.53 (s, 2 H), 4.13 (dd, *J* = 5.2, 1.5 Hz, 2 H), 3.91 (bs, 1 H), 3.81 (s, 3 H); ^{13}C NMR δ 174.64, 141.34, 138.19, 131.97, 128.48, 128.15, 128.08, 127.86, 127.74, 126.12, 78.10, 72.41, 69.76, 53.55; MS (EI) *m/z* (intensity) 253 ($[M-CO_2Me]^+$, 18), 105 (13), 91 (100); HRMS (EI) *m/z* calculated for $C_{17}H_{17}O_2$ (M-CO_2Me) 253.1229, found 253.1224.



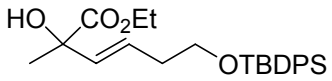
144

(*E*,*E*)-2-Hydroxy-6-methyl-2-phenyldodeca-3,5-dienoic acid methyl ester (**144**). According to the General Protocol B, Cp_2ZrHCl (0.24 g, 0.91 mmol), **143**[218] (0.14 g, 0.91 mmol), Me_2Zn (0.46 mL, 0.91 mmol, 2.0 M in toluene) and **134** (87 μL, 0.61 mmol) afforded **144** (0.17 g, 88%) as a colorless oil: IR (neat) 3504, 2955, 2928, 2856, 1732, 1652, 1493, 1449, 1436, 1384, 1250, 1198, 1139 cm^{-1}; ^1H NMR δ 7.54-7.51 (m, 2 H), 7.36-7.30 (m, 3 H), 6.81 (dd, *J* = 15.0, 11.1 Hz, 1 H), 6.10 (d, *J* = 15.1 Hz, 1 H), 5.94 (d, *J* = 11.1 Hz, 1 H), 3.89 (bs, 1 H), 3.81 (s, 3 H), 2.06 (t, *J* = 7.2 Hz, 2 H), 1.77 (s, 3 H), 1.45-1.38 (m, 2 H), 1.34-1.29 (m, 6 H), 0.91-0.87 (m, 3 H); ^{13}C NMR δ 175.13, 141.88, 141.72, 129.84, 128.50, 128.12, 127.33, 126.28, 123.50, 78.49, 53.58, 40.14, 31.93, 29.19, 27.93, 22.76, 16.89, 14.26; MS (EI) *m/z* (intensity) 316 (M^+, 5), 257 (76), 171 (18), 105 (100), 91 (19); HRMS (EI) *m/z* calculated for $C_{20}H_{28}O_3$ 316.2038, found 316.2044.



146

(*E*)-2-Hydroxy-2-methyloct-3-enoic acid ethyl ester (**146**). According to the General Protocol B, Cp_2ZrHCl (0.24 g, 0.91 mmol), **108** (0.10 mL, 0.91 mmol), Me_2Zn (0.46 mL, 0.91 mmol, 2.0 M in toluene) and **145** (67 μL, 0.61 mmol) afforded **146** (0.11 g, 93%) as a colorless oil: IR (neat) 3518, 2959, 2930, 2873, 1730, 1449, 1372, 1256, 1203, 1140, 1107 cm^{-1}; ^1H NMR δ 5.81 (dt, *J* = 15.4, 6.8 Hz, 1 H), 5.56 (dt, *J* = 15.4, 1.3 Hz, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 3.32 (s, 1 H), 2.02 (q, *J* = 6.7 Hz, 2 H), 1.45 (s, 3 H), 1.39-1.25 (m, 7 H), 0.89 (t, *J* = 6.9 Hz, 3 H); ^{13}C NMR δ 176.14, 131.64, 131.03, 74.30, 62.10, 31.84, 31.30, 26.06, 22.27, 14.26, 14.02; MS (EI) *m/z* (intensity) 200 (M^+, 0.2), 180 (1), 127 (100), 111 (8); HRMS (EI) *m/z* calculated for $C_{11}H_{20}O_3$ 200.1412, found 200.1422.

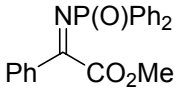


147

(*E*)-6-(*tert*-Butyldiphenylsilanyloxy)-2-hydroxy-2-methylhex-3-enoic acid ethyl ester (**147**). According to the General Protocol B, Cp_2ZrHCl (0.24 g, 0.91 mmol), **125** (0.28 g, 0.91 mmol), Me_2Zn (0.46 mL, 0.91 mmol, 2.0 M in toluene) and **145** (67 μL, 0.61 mmol) afforded **147** (0.20

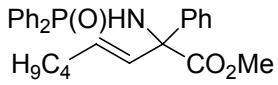
[218] See pages 90-91 for the preparation of **143**.

g, 75%) as a colorless oil: IR (neat) 3520, 3071, 3048, 2932, 2858, 1730, 1473, 1428, 1259, 1206, 1188, 1112 cm^{-1}; ^1H NMR δ 7.69-7.65 (m, 4 H), 7.43-7.36 (m, 6 H), 5.88 (dt, J = 15.5, 6.9 Hz, 1 H), 5.67 (dt, J = 15.5, 1.2 Hz, 1 H), 4.28-4.13 (m, 2 H), 3.70 (t, *J* = 6.5 Hz, 2 H), 3.24 (s, 1 H), 2.31 (qd, *J* = 6.7, 1.2 Hz, 2 H), 1.47 (s, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 1.05 (s, 9 H); ^{13}C NMR δ 175.97, 135.72, 133.98, 133.58, 129.74, 127.78, 127.46, 74.34, 63.40, 62.17, 35.59, 26.91, 26.13, 19.35, 14.26; MS (EI) *m/z* (intensity) 408 ($[M-H_2O]^+$, 0.4), 369 (9), 339 (11) 293 (7), 229 (18), 199 (100), 135 (23); HRMS (EI) *m/z* calculated for $C_{25}H_{32}O_3Si$ (M-H_2O) 408.2121, found 408.2135.



148

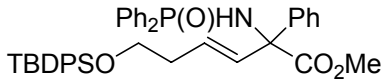
(*P*,*P*-Diphenylphosphinoylimino)phenylacetic acid methyl ester (**148**). To a cooled (0 °C) solution of **134** (0.65 mL, 4.6 mmol), **118** (1.7 g, 8.0 mmol) and Et_3N (3.2 mL, 23 mmol) in dry CH_2Cl_2 (20 mL) was dropwise added a solution of $TiCl_4$ (0.50 mL, 4.6 mmol) in dry CH_2Cl_2 (5.0 mL). The reaction mixture was warmed to r.t., stirred for 24 h, diluted with ether (0.10 L), filtered through a pad of Celite/Florisil (1:1) and concentrated. The crude residue was purified by chromatography on SiO_2 (3:7, hexanes/EtOAc) followed by precipitation from a minimal amount of CH_2Cl_2 with dry hexanes to give **148** (0.66 g, 40%) as a colorless solid: mp 118.5-120.5 °C (hexanes/CH_2Cl_2); IR (KBr) 3058, 2963, 1746, 1737, 1649, 1619, 1591, 1575, 1450, 1437, 1430, 1303, 1199, 1123, 1105; ^1H NMR δ 7.99-7.91 (m, 6 H), 7.63-7.43 (m, 9 H), 4.06 (s, 3 H); ^{13}C NMR δ 170.32, 170.20, 166.20, 165.99, 133.81, 133.78, 131.87, 131.83, 131.72, 131.59, 129.00, 128.87, 128.55, 128.38, 53.37; MS (EI) *m/z* (intensity) 363 (M^+, 0.2), 304 (27), 201 (100), 103 (9); HRMS (EI) *m/z* calculated for $C_{21}H_{18}NO_3P$ 363.1024, found 363.1025.



149

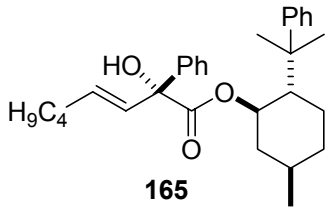
2-(*P*,*P*-Diphenylphosphinoylamino)-2-phenyloct-3-enoic acid methyl ester (149) General Protocol C. To a suspension of Cp_2ZrHCl (0.11 g, 0.41 mmol) in dry CH_2Cl_2 (2.0 mL) was added **108** (47 μL, 0.41 mmol) and the reaction mixture was stirred for 10 min at r.t. The solvent was removed in vacuo, and the residue was dissolved in dry toluene (2.0 mL), cooled to -78 °C, treated with Me_2Zn (0.21 mL, 0.41 mmol, 2.0 M in toluene) and warmed to 0 °C. After addition of **148** (0.10 g, 0.28 mmol) the reaction mixture was stirred for 1 h, quenched with sat. NH_4Cl,

diluted with EtOAc, and filtered through Celite. The aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (3:7, hexanes/EtOAc containing 1% v/v Et_3N) to give **149** (0.11 g, 92%) as a colorless oil: IR (neat) 3376, 3058, 2955, 2928, 2858, 1734, 1438, 1391, 1242, 1207, 1122, 1050 cm^{-1}; ^1H NMR δ 7.85-7.75 (m, 4 H), 7.46-7.33 (m, 8 H), 7.24-7.17 (m, 3 H), 5.96 (dt, *J* = 15.6, 1.5 Hz, 1 H), 5.53 (dt, *J* = 15.6, 6.6 Hz, 1 H), 4.41 (d, *J* = 6.1 Hz, 1 H), 3.79 (s, 3 H), 1.85-1.76 (m, 2 H), 1.29-1.05 (m, 4 H), 0.82 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR δ 174.25, 174.18, 139.79, 136.44, 135.54, 135.04, 133.86, 133.32, 131.92, 131.80, 131.50, 131.37, 131.08, 129.07, 128.34, 128.17, 128.10, 127.93, 127.88, 127.76, 127.58, 68.25, 53.01, 31.69, 30.37, 22.14, 13.73; MS (EI) *m/z* (intensity) 447 (M^+, 2), 388 (57), 201 (100); HRMS (EI) *m/z* calculated for $C_{27}H_{30}NO_3P$ 447.1963, found 447.1984.



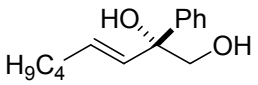
150

2-(*P*,*P*-Diphenylphosphinoylamino)-6-(*tert*-butyldiphenylsilanyloxy)-2-phenylhex-3-enoic acid methyl ester (150). According to the General Protocol C, Cp_2ZrHCl (0.11 g, 0.41 mmol), **125** (0.13 g, 0.41 mmol), Me_2Zn (0.21 mL, 0.41 mmol, 2.0 M in toluene) and **148** (0.10 g, 0.28 mmol) afforded **150** (0.17 g, 93%) as a colorless oil: IR (neat) 3372, 3056, 2953, 2931, 2857, 1735, 1472, 1437, 1389, 1242, 1208, 1110 cm^{-1}; ^1H NMR δ 7.82-7.74 (m, 4 H), 7.63-7.59 (m, 4 H), 7.45-7.19 (m, 17 H), 6.08 (dt, *J* = 15.7, 1.3 Hz, 1 H), 5.62 (dt, *J* = 15.6, 6.8 Hz, 1 H), 4.42 (d, *J* = 5.9 Hz, 1 H), 3.77 (s, 3 H), 3.52-3.40 (m, 2 H), 2.20-1.97 (m, 2 H), 1.00 (s, 9 H); ^{13}C NMR δ 174.23, 174.16, 139.39, 139.32, 135.46, 135.29, 134.88, 133.83, 133.78, 133.60, 133.14, 132.88, 131.91, 131.79, 131.47, 131.35, 131.13, 131.04, 129.48, 128.36, 128.19, 128.13, 127.93, 127.67, 127.54, 68.24, 62.76, 53.14, 35.43, 26.71, 19.08; MS (EI) *m/z* (intensity) 673 (M^+, 1), 616 (68), 536 (9), 399 (9), 358 (21), 201 (100), 135 (52); HRMS (EI) *m/z* calculated for $C_{41}H_{44}NO_4SiP$ 673.2777, found 673.2756.



165

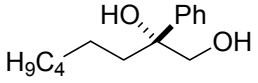
(*2R*,*3E*)-2-Hydroxy-2-phenyloct-3-enoic acid (-)-8-phenylmenthyl ester (**165**). To a suspension of Cp_2ZrHCl (80 mg, 0.31 mmol) in dry CH_2Cl_2 (2.0 mL) was added **108** (36 μL, 0.31 mmol). The reaction stirred for 10 min. at r.t., solvent was removed in vacuo, and the residue was dissolved in dry toluene (2.0 mL), cooled to -78 °C, treated with Me_2Zn (0.16 mL, 0.31 mmol, 2.0 M in toluene) and warmed to -20 °C. After addition of **163** (75 mg, 0.21 mmol), the reaction mixture was stirred for 12 h, quenched with sat. NH_4Cl, diluted with EtOAc, and filtered through Celite. The aqueous layer was extracted with EtOAc (2x) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (19:1, hexanes/EtOAc) to give the allylic alcohol **165** (71 mg, 77%) as a colorless oil: $[\alpha]_D$ -56.1, (*c* 0.92, EtOH); IR (neat) 3499, 3058, 2956, 2925, 2870, 1719, 1448, 1246, 1151 cm^{-1}; ^1H NMR δ 7.65-7.62 (m, 2 H), 7.46-7.27 (m, 8 H), 6.19-6.03 (m, 2 H), 4.98 (td, *J* = 10.7, 4.3 Hz, 1 H), 3.15 (bs, 1 H), 2.37-2.30 (m, 2 H), 2.16-2.01 (m, 2 H), 1.75-1.47 (m, 8 H), 1.23 (s, 3 H), 1.18-1.06 (m, 8 H), 1.04 (d, *J* = 12.9 Hz, 3 H); ^{13}C NMR (MeOD) δ 173.19, 151.05, 141.45, 132.49, 130.23, 128.30, 127.97, 126.65, 125.69, 125.51, 78.27, 77.81, 50.35, 41.33, 39.96, 34.60, 32.08, 31.48, 31.44, 27.29, 27.18, 25.90, 22.39, 21.88, 14.13; MS (EI) *m/z* (intensity) 448 (M^+, 0.4), 216 (53), 189 (50), 143 (45), 119 (100), 105 (62), 91 (67); HRMS (EI) *m/z* calculated for $C_{30}H_{40}O_3$ 448.2977, found 448.2983.



166

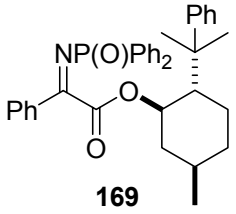
(*2R*,*3E*)-2-Phenyloct-3-ene-1,2-diol (**166**). The crude residue from the preparation of **165** (0.33 mmol scale) was dissolved in dry Et_2O (1.5 mL), cooled to -78 °C, treated with $LiAlH_4$ (0.72 mL, 0.72 mmol, 1.0 M in Et_2O), warmed to room temperature and stirred for 2 h. The reaction was cooled to 0 °C, quenched with sat. NH_4Cl, diluted with EtOAc, and filtered through Celite. The aqueous layer was extracted with EtOAc (2x) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (3:1, hexanes/EtOAc) to give the auxilliary **161** (42 mg, 92%) and the desired product **166**

(42 mg, 87%, >99% ee by HPLC analysis (Chiralcel OD, 97.5:2.5 hexanes/*i*-PrOH) R_t **(+)-166** 19.1 min, **(-)-166** 20.5 min[219]) as a colorless solid: mp 49.0-51.5 °C (hexanes/EtOAc); $[\alpha]_D$ +16.9, (*c* 0.65, EtOH); IR (neat) 3373, 1956, 2926, 2856, 1448, 1378, 1265, 1067 cm^{-1}; ^1H NMR (CD_3OD) δ 7.46 (d, *J* = 7.5 Hz, 2 H), 7.30 (t, *J* = 7.2 Hz, 2 H), 7.20 (t, *J* = 7.4 Hz, 1 H), 5.82 (d, *J* = 16.0 Hz, 1 H), 5.69 (dt, *J* = 15.6, 6.4 Hz, 1 H), 3.70 (s, 2 H), 2.12-2.05 (m, 2 H), 1.42-1.27 (m, 4 H), 0.89 (t, *J* = 6.9 Hz, 3 H); ^{13}C NMR (CD_3OD) δ 145.64, 134.66, 132.03, 128.84, 127.74, 127.25, 77.92, 70.64, 33.31, 32.62, 23.26, 14.28; MS (EI) *m/z* (intensity) 220 (M^+, 0.8), 202 (33), 189 (67), 173 (92), 155 (45), 145 (75), 129 (48), 133 (85), 129 (50), 105 (87), 91 (100); HRMS (EI) *m/z* calculated for $C_{14}H_{18}O$ (M-H_2O) 202.1358, found 202.1364.



167

(*R*)-2-Phenyloctane-1,2-diol (**167**).[220] To a solution of **166** (77 mg, 0.18 mmol) in EtOAc (3.0 mL) was added Rh/Al_2O_3 (36 mg, 5 wt % Rh on Al_2O_3) and the reaction vessel was evacuated, purged with H_2 (1 atm) and stirred for 1 h. The mixture was filtered through a plug of Celite and concentrated, and the residue was purified by chromatography on SiO_2 (3:1, Hexanes/EtOAc) to give **167** (75 mg, 97%, >99% ee by HPLC analysis (Chiralcel OD, 97.5:2.5 hexanes/*i*-PrOH) R_t **(+)-167** 18.3 min, **(-)-167** 20.1 min[221]) as a colorless solid: mp 35.5-37.0 °C (hexanes/EtOAc); $[\alpha]_D$ +2.15, (*c* 1.1, EtOH); ^1H NMR δ 7.43-7.35 (m, 4 H), 7.30-7.24 (m, 1 H), 3.83 (dd, *J* = 11.0, 2.7 Hz, 1 H), 3.71-3.65 (m, 1 H), 2.66 (s, 1 H), 1.85-1.76 (m, 3 H), 1.34-1.21 (m, 7 H), 1.10-0.99 (m, 1 H), 0.84 (t, *J* = 6.7 Hz, 3 H).

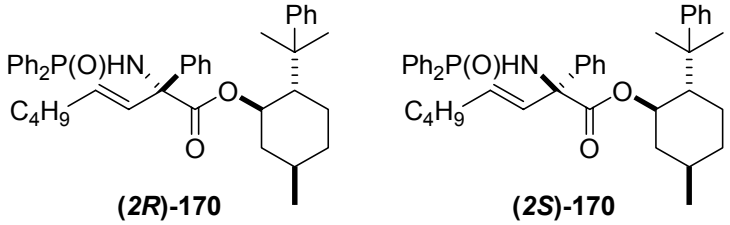


169

(*P*,*P*-Diphenylphosphinoylimino)phenylacetic acid (-)-8-phenylmenthyl ester (**169**). To a cooled (0 °C) solution of **163** (0.85 g, 2.3 mmol), **118** (1.3 g, 5.8 mmol) and Et_3N (0.97 mL, 7.0 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise a solution of $TiCl_4$ (0.26 mL, 2.3 mmol) in dry CH_2Cl_2 (5.0 mL). The reaction mixture was warmed to r.t., stirred for 36 h, diluted with

[219] The peak for the minor enantiomer was inferred from the HPLC trace of (+/-)-**166**.
[220] Vanhessche, K. P. M.; Sharpless, K. B. *J. Org. Chem.* **1996**, *61*, 7978.
[221] The peak for the minor enantiomer was inferred from the HPLC trace of (+/-)-**167**.

ether (0.10 L), filtered through a pad of Celite/Florisil (1:1) and concentrated. The crude residue was purified by chromatography on SiO_2 (7:3, hexanes/EtOAc) to give **169** (0.91 g, 69%) as a colorless foam: $[\alpha]_D$ -19.7 (*c* 0.44, $CHCl_3$); IR (KBr) 3057, 2958, 2924, 2869, 1731, 1631, 1594, 1577, 1483, 1449, 1293, 1216, 1180, 1124, 1108; ^{1}H NMR (600 MHz) δ 8.06 (dd, *J* = 11.9, 6.9 Hz, 2 H), 7.90 (d, *J* = 7.9 Hz, 2 H), 7.85 (dd, *J* = 12.2, 7.1 Hz, 2 H), 7.57 (t, *J* = 7.3 Hz, 1 H), 7.51-7.43 (m, 8 H), 7.08-7.07 (m, 2 H), 6.89-6.88 (m, 3 H), 5.04 (td, *J* = 10.7, 4.0 Hz, 1 H), 2.71 (dq, *J* = 12.2, 2.4 Hz, 1 H), 1.96 (ddd, *J* = 12.2, 10.7, 3.2 Hz, 1 H), 1.60-1.54 (m, 2 H), 1.42 (dq, *J* = 13.6, 3.2 Hz, 1 H), 1.27 (s, 3 H), 1.20 (q, *J* = 12.1 Hz, 1 H), 1.17 (s, 3 H), 1.07 (dq, *J* = 12.9, 3.1 Hz, 1 H), 0.96 (d, *J* = 6.3 Hz, 3 H), 0.84 (dq, *J* = 12.4, 3.2 Hz, 1 H); ^{13}C NMR δ 169.87, 169.76, 164.27, 164.06, 151.30, 134.16, 134.05, 133.87, 133.76, 133.24, 132.38, 132.16, 132.04, 131.97, 131.68, 131.65, 131.46, 131.33, 129.07, 128.49, 128.36, 128.19, 127.52, 125.21, 124.67, 79.47, 50.84, 40.59, 39.94, 34.61, 31.54, 27.38, 27.12, 24.95, 21.82; MS (EI) *m/z* (intensity) 563 (M^+, 0.8), 445 (1), 350 (8), 304 (13), 201 (100), 119 (33), 103 (15), 91 (18); HRMS (EI) *m/z* calculated for $C_{36}H_{38}NO_3P$ 563.2589, found 563.2576.

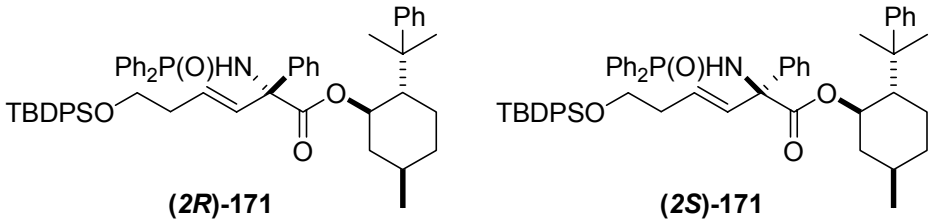


(2*R*)-170 **(2*S*)-170**

(2*R*)-2-(*P*,*P*-Diphenylphosphinoylamino)-2-phenyloct-3-enoic acid (-)-8-phenylmenthyl ester ((2*R*)-170) and (2*S*)-2-(*P*,*P*-Diphenylphosphinoylamino)-2-phenyloct-3-enoic acid (-)-8-phenylmenthyl ester ((2*S*)-170). **General Protocol D**. To a suspension of Cp_2ZrHCl (0.23 g, 0.89 mmol) in dry CH_2Cl_2 (4.0 mL) was added **108** (0.10 mL, 0.89 mmol) and the reaction mixture was stirred for 10 min. at r.t. The solvent was removed in vacuo, and the residue was dissolved in dry toluene (2.0 mL), cooled to -78 °C, and treated with Me_2Zn (0.44 mL, 0.89 mmol, 2.0 M in toluene). Upon warming to -40 °C, the solution was transferred via cannula to a pre-cooled (-40 °C) solution of **169** (0.25 g, 0.44 mmol) and $ClTi(O\text{-}iPr)_3$ (0.44 mL, 0.44 mmol, 1.0 M in CH_2Cl_2) in dry toluene (1.0 mL). The organometallic-containing flask was washed with dry toluene (2 x 0.50 mL) and these washing were transferred to the imine flask via cannula. The reaction mixture was stirred for 24 h, quenched with sat. NH_4Cl, diluted with EtOAc, and filtered through Celite. The aqueous layer was extracted with EtOAc (2x) and the combined organic

layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (3:2, hexanes/EtOAc containing 1% v/v Et_3N) to give **(2*R*)-170** and **(2*S*)-170** (0.20 g, 70%, *dr* 7.8:1) as a colorless foam. The diastereomers were separated by chromatography on deactivated SiO_2 (17:3, hexanes/EtOAc containing 1% v/v Et_3N): **(*2R*)-170** (major isomer): $[\alpha]_D$ -14.2 (*c* 0.89, $CHCl_3$); IR (neat) 3410, 3054, 2961, 2929, 1720, 1635, 1439, 1265, 1208, 1123 cm^{-1}; ^1H NMR δ 7.85-7.77 (m, 2 H), 7.73-7.66 (m, 2 H), 7.46-7.36 (m, 6 H), 7.30-7.27 (m, 2 H), 7.18-7.07 (m, 8 H), 5.98-5.81 (m, 2 H), 4.85 (dt, *J* = 10.6, 4.2 Hz, 1 H), 4.49 (d, *J* = 7.5 Hz, 1 H), 2.08-1.94 (m, 3 H), 1.80-1.71 (m, 1 H), 1.47-1.40 (m, 2 H), 1.33-1.25 (m, 4 H), 1.22-1.14 (m, 1 H), 1.08 (s, 3 H), 0.99-0.85 (m, 5 H), 0.84 (d, *J* = 6.3 Hz, 3 H), 0.81 (s, 3 H), 0.75-0.63 (m, 1 H); ^{13}C NMR δ 172.50, 172.39, 150.02, 139.15, 139.12, 135.97, 135.43, 135.17, 133.72, 133.45, 131.83, 131.76, 131.70, 131.63, 131.18, 130.94, 129.23, 129.19, 128.31, 128.16, 128.00, 127.82, 127.66, 125.54, 125.21, 78.23, 68.15, 50.41, 41.08, 40.05, 34.26, 31.84, 31.26, 30.68, 30.21, 27.42, 22.79, 22.19, 21.60, 13.82; MS (EI) *m/z* (intensity) 647 (M^+, 1), 432 (2), 415 (2), 388 (100), 201 (69), 119 (39), 105 (35); HRMS (EI) *m/z* calculated for $C_{42}H_{50}NO_3P$ 647.3528, found 647.3526.

(*2S*)-170 (minor isomer): $[\alpha]_D$ -15.5 (*c* 0.89, $CHCl_3$); IR (neat) 3373, 2955, 2924, 2854, 1722, 1439, 1212, 1122 cm^{-1}; ^1H NMR (600 MHz) δ 7.83-7.80 (m, 4 H), 7.50-7.48 (m, 3 H), 7.44-7.41 (m, 3 H), 7.37-7.36 (m, 2 H), 7.28-7.25 (m, 2 H), 7.23-7.22 (m, 1 H), 7.05-7.04 (m, 2 H), 6.99-6.97 (m, 3 H), 5.82 (dt, *J* = 15.5, 1.5 Hz, 1 H), 5.47 (dt, *J* = 15.5, 6.6 Hz, 1 H), 4.91 (dt, *J* = 10.6, 4.1 Hz, 1 H), 4.02 (d, *J* = 6.6 Hz, 1 H), 2.12-2.09 (m, 1 H), 1.95-1.90 (m, 1 H), 1.75-1.66 (m, 2 H), 1.55-1.53 (m, 2 H), 1.49-1.43 (m, 1 H), 1.39-1.37 (m, 1 H), 1.16-1.11 (m, 2 H), 1.15 (s, 3 H), 1.11 (s, 3 H), 1.04-0.98 (m, 4 H), 0.89 (d, *J* = 6.5 Hz, 3 H), 0.79 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR δ 172.53, 172.46, 150.46, 139.63, 139.57, 137.26, 135.96, 135.42, 134.27, 133.68, 132.02, 131.90, 131.75, 131.62, 131.26, 131.08, 130.80, 128.98, 128.94, 128.36, 128.18, 128.00, 127.90, 127.80, 127.68, 125.39, 125.05, 78.09, 68.24, 50.36, 41.20, 40.04, 34.50, 31.70, 34.42, 30.27, 28.94, 27.34, 24.78, 22.29, 21.71, 13.83; MS (EI) *m/z* (intensity) 647 (M^+, 0.7), 433 (3), 388 (100), 201 (62), 119 (28), 105 (26); HRMS (EI) *m/z* calculated for $C_{42}H_{50}NO_3P$ 647.3528, found 647.3532.

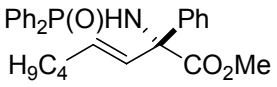


(2*R*)-171 **(2*S*)-171**

(2*R*)-2-(*P*,*P*-Diphenylphosphinoylamino)-6-(*tert*-butyldiphenylsilanyloxy)-2-phenylhex-3-enoic acid (-)-8-phenylmenthyl ester ((2*R*)-171) and (2*S*)-2-(*P*,*P*-Diphenylphosphinoyl-amino)-6-(*tert*-butyldiphenylsilanyloxy)-2-phenylhex-3-enoic acid (-)-8-phenylmenthyl ester ((2*S*)-171). According to the General Protocol D, Cp_2ZrHCl (0.27 g, 1.1 mmol), **125** (0.33 g, 1.1 mmol), Me_2Zn (0.53 mL, 1.1 mmol, 2.0 M in toluene), $ClTi(O\text{-}iPr)_3$ (0.53 mL, 0.53 mmol, 1.0 M in CH_2Cl_2) and **169** (0.30 g, 0.53 mmol) afforded **(2*R*)-171** and **(2*S*)-171** (0.39 g, 84%, *dr* 7.4:1) as a colorless foam: **(*2R*)-171** (major isomer): $[\alpha]_D$ -11.7 (*c* 0.94, $CHCl_3$); IR (neat) 3364, 3057, 2928, 2858, 1722, 1493, 1440, 1212, 1110 cm^{-1}; ^1H NMR δ 7.80-7.71 (m, 4 H), 7.69-7.64 (m, 4 H), 7.46-7.24 (m, 15 H), 7.18-7.06 (m, 7 H), 6.04 (d, *J* = 15.7 Hz, 1 H), 5.87 (dt, *J* = 15.6, 6.6 Hz, 1 H), 4.84 (dt, *J* = 10.5, 4.1 Hz, 1 H), 4.40 (d, *J* = 7.1 Hz, 1 H), 3.64-3.53 (m, 2 H), 2.33-2.15 (m, 2 H), 2.06-1.99 (m, 1 H), 1.81-1.72 (m, 1 H), 1.47-1.39 (m, 2 H), 1.21-1.13 (m, 1 H), 1.07 (s, 3 H), 1.05 (s, 9 H), 0.99-0.84 (m, 2 H), 0.81-0.80 (m, 6 H), 0.75-0.62 (m, 1 H); ^{13}C NMR δ 172.47, 172.38, 150.18, 138.74, 138.71, 135.52, 135.25, 135.18, 133.86, 133.54, 133.46, 132.19, 131.84, 131.81, 131.72, 131.69, 131.26, 131.04, 129.56, 128.47, 128.20, 128.11, 128.03, 127.94, 127.88, 127.81, 127.74, 127.63, 125.58, 125.24, 78.35, 68.22, 63.21, 50.34, 40.98, 40.06, 35.71, 34.27, 31.33, 30.09, 27.46, 26.86, 22.95, 21.65, 19.17; MS (ESI) *m/z* (intensity) 897 ($[M+Na]^+$, 65), 874 ($[M+H]^+$, 100); HRMS (ESI) *m/z* calculated for $C_{56}H_{64}NO_4NaSiP$ (M+Na) 896.4240, found 896.4240.

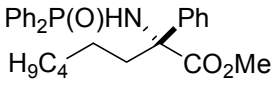
(*2S*)-171 (minor isomer): $[\alpha]_D$ -8.1 (*c* 0.53, $CHCl_3$); IR (neat) 3322, 3056, 2957, 2926, 2855, 1723, 1591, 1440, 1388, 1213, 1110 cm^{-1}; ^1H NMR δ 7.83-7.74 (m, 4 H), 7.59-7.56 (m, 4 H), 7.51-7.48 (m, 2 H), 7.42-7.20 (m, 15 H), 7.03-6.92 (m, 5 H), 5.89 (d, *J* = 15.7 Hz, 1 H), 5.50 (dt, *J* = 15.6, 6.7 Hz, 1 H), 4.90 (dt, *J* = 10.7, 4.2 Hz, 1 H), 3.98 (d, *J* = 5.9 Hz, 1 H), 3.42-3.28 (m, 2 H), 2.12-2.01 (m, 2 H), 1.96-1.84 (m, 2 H), 1.56-1.52 (m, 2 H), 1.41-1.36 (m, 1 H), 1.11 (s, 3 H), 1.06 (s, 3 H), 1.06-1.03 (m, 1 H), 0.98 (s, 9 H), 0.88 (d, *J* = 6.4 Hz, 3 H), 0.89-0.84 (m, 1 H), 0.84-0.72 (m, 1 H); ^{13}C NMR δ 172.41, 172.34, 150.52, 139.31, 139.24, 135.77. 135.52. 135.34. 134.07. 133.98. 133.57. 132.03. 131.91. 131.70. 131.57. 131.29. 131.10. 130.97. 130.93. 129.48.

128.35, 128.19, 128.02, 127.89, 127.87, 127.82, 127.57, 125.39, 125.02, 78.14, 68.22, 62.82, 50.30, 41.18, 40.00, 35.42, 34.53, 31.45, 28.75, 27.34, 26.83, 24.91, 21.74, 19.13; MS (ESI) *m/z* (intensity) 874 ($[M+H]^+$, 50), 371 (25); HRMS (ESI) *m/z* calculated for $C_{56}H_{65}NO_4SiP$ (M+H) 874.4421, found 874.4474.



(+)-149

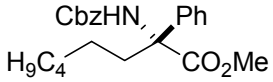
(+)-(*2R*)-2-(*P*,*P*-Diphenylphosphinoylamino)-2-phenyloct-3-enoic acid methyl ester ((+)-149). To a solution of KO*t*-Bu (0.14 g, 1.2 mmol) in dry THF (2.0 mL) was added H_2O (6.0 μL, 0.33 mmol). The suspension was stirred for 10 min, treated with a solution of **(2*R*)-170** (0.10 g, 0.15 mmol) in dry THF (1.0 mL) and heated at 70 °C for 5 h. The reaction mixture was cooled to r.t., quenched with 10% HCl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. A solution of the residue in MeOH (1.5 mL) was treated with $TMSCHN_2$ (0.30 mL, 0.60 mmol, 2.0 M in hexanes), stirred for 15 min, quenched at 0 °C with 10% HCl, and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude residue was purified by chromatography on SiO_2 (1:1, hexanes/EtOAc) to give **(+)-149** (58 mg, 84%) as a colorless oil: $[\alpha]_D$ +4.4 (*c* 0.41, $CHCl_3$).



172

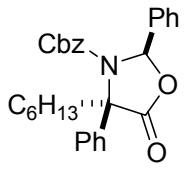
(+)-(*2R*)-2-(*P*,*P*-Diphenylphosphinoylamino)-2-phenyloctanoic acid methyl ester (172). A mixture of **(+)-149** (0.12 g, 0.28 mmol) and PtO_2 (6.0 mg, 26 μmol) in MeOH (3.0 mL) was evacuated, flushed with H_2 (1 atm), and stirred for 1.5 h. The reaction mixture was filtered through Celite, concentrated and purified by chromatography on SiO_2 (1:1, hexanes/EtOAc) to give **172** (0.12 g, quant.) as a colorless oil: $[\alpha]_D$ +2.15 (*c* 0.93, $CHCl_3$); IR (neat) 3369, 3058, 2954, 2928, 2856, 1732, 1438, 1392, 1245, 1208, 1147, 1122, 1109, 1073 cm^{-1}; ^1H NMR δ 7.82-7.75 (m, 2 H), 7.56-7.39 (m, 5 H), 7.31-7.27 (m, 1 H), 7.23-7.15 (m, 4 H), 7.10-7.07 (m, 3 H), 4.69 (d, *J* = 8.1 Hz, 1 H), 3.69 (s, 3 H), 2.59 (dt, *J* = 12.9, 4.2 Hz, 1 H), 2.23 (dt, *J* = 12.3, 4.2 Hz, 1 H), 1.75-1.65 (m, 1 H), 1.33-1.17 (m, 6 H), 1.05-0.90 (m, 1 H), 0.87 (t, *J* = 6.7 Hz, 3 H); ^{13}C NMR δ 175.12, 174.98, 140.80, 140.76, 135.43, 133.75, 132.07, 131.95, 131.57, 131.54, 131.31, 131.18, 130.78, 130.75, 128.43, 128.26, 127.97, 127.80, 127.62, 127.50, 126.51, 66.92, 52.89,

36.40, 31.58, 29.19, 24.32, 22.54, 13.96; MS (EI) *m/z* (intensity) 449 (M^+, 6), 391 (43), 390 (100), 364 (32), 202 (22), 201 (67), 77 (21); HRMS (EI) *m/z* calculated for $C_{27}H_{32}NO_3P$ 449.2120, found 449.2127.



(-)-173

(-)-(*2R*)-2-Benzyloxycarbonylamino-2-phenyloctanoic acid methyl ester ((-)-173). To a solution of **(+)-172** (0.12 g, 0.28 mmol) in MeOH (1.5 mL) was added a solution of HCl (1.5 mL, 1.0 M in MeOH). The reaction mixture was stirred for 12 h, concentrated and dissolved in EtOAc (2.0 mL) and H_2O (2.0 mL), cooled to 0 °C, treated with $NaHCO_3$ (0.12 g, 1.4 mmol) and Cbz-Cl (48 μL, 0.33 mmol) and stirred for 1.5 h. The solution was diluted with H_2O and EtOAc and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude residue was purified by chromatography on SiO_2 (19:1, hexanes/EtOAc) to give **(-)-173** (78 mg, 73%, 96.5% ee by HPLC (Chiralcel OD, 99.5:0.5, hexanes/*i*-PrOH) R_t **(-)-173** 17.1 min, **(+)-173** 19.4 min)) as a colorless solid: mp 66.0-68.5 °C (hexanes/EtOAc); $[\alpha]_D$ -32.4 (*c* 0.51, $CHCl_3$); IR (neat) 3420, 3063, 3032, 2955, 2928, 2858, 1726, 1495, 1453, 1319, 1253, 1087, 1069, 1036 cm^{-1}; ^1H NMR δ 7.53-7.27 (m, 10 H), 6.46 (bs, 1 H), 5.08, 5.00 (AB, *J* = 11.9 Hz, 2 H), 3.68 (s, 3 H), 2.77 (bm, 1 H), 2.49-2.41 (m, 1 H), 1.37-1.29 (m, 7 H), 1.08-1.01 (m, 1 H), 0.91 (t, *J* = 6.3 Hz, 3 H); ^{13}C NMR δ 173.2, 153.7, 140.2, 136.5, 128.4, 127.9, 127.7, 125.9, 66.4, 65.3, 53.2, 33.0, 31.6, 29.1, 24.1, 22.5, 14.0; MS (EI) *m/z* (intensity) 384 ($[M+H]^+$, 0.5), 383 (M^+, 2), 325 (38), 324 (87), 281 (42), 280 (100), 254 (20), 234 (25), 216 (68), 91 (100); HRMS (EI) *m/z* calculated for $C_{23}H_{29}NO_4$ 383.2097, found 383.2106.

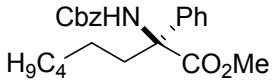


175

(2*R*,4*R*)-benzyl 4-hexyl-5-oxo-2,4-diphenyloxazolidine-3-carboxylate (175). To a solution of **174**[222] (0.20 g, 0.54 mmol) and HMPA (93 μL, 0.54 mmol) in dry THF (8.0 mL) at -78 °C was added NaHMDS (0.32 mL, 0.64 mmol, 2.0 M in THF). The reaction mixture was stirred for 20

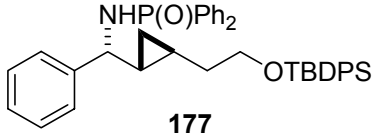
[222] O'Donnell, M. J.; Fang, Z.; Ma, X.; Huffman, J. C. *Heterocycles* **1997**, *46*, 617.

min and freshly prepared hexyl triflate[223] (0.38 g, 1.6 mmol) was added as a solution in THF (2.0 mL). After 3 h, the solution was quenched with sat. NH_4Cl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude residue was purified by chromatography on SiO_2 (19:1, hexanes/EtOAc) to give **175** (0.18 g, 73%) as a colorless oil: $[\alpha]_D$ +29.4 (*c* 1.1, $CHCl_3$); IR (neat) 3064, 3036, 2928, 2857, 1796, 1716, 1495, 1451, 1401, 1345, 1234, 1174, 1138, 1113, 1028 cm^{-1}; ^1H NMR (DMSO-d_6, 80 °C) δ 7.51-7.47 (m, 2 H), 7.39-7.34 (m, 8 H), 7.29-7.27 (m, 3 H), 7.17-7.12 (m, 2 H), 6.90 (s, 1 H), 5.13, 5.07 (AB, *J* = 12.4 Hz, 2 H), 2.70-2.65 (m, 1 H), 2.36-2.27 (m, 1 H), 1.26-1.24 (m, 8 H), 0.87 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (DMSO-d_6, 80 °C) δ 171.9, 151.7, 137.9, 136.1, 135.1, 129.2, 127.8, 127.7, 127.6, 127.4, 126.6, 125.6, 88.5, 67.6, 66.7, 36.4, 30.3, 27.6, 23.3, 21.3, 13.1; MS (EI) *m/z* (intensity) 457 (M^+, 1), 372 (23), 328 (16), 278 (5), 193 (5), 91 (100); HRMS (EI) *m/z* calculated for $C_{29}H_{31}NO_4$ 457.2253, found 457.2255.



(+)-173

(+)-(*2S*)-2-Benzyloxycarbonylamino-2-phenyloctanoic acid methyl ester ((+)-173). To a solution of **175** (90 mg, 0.20 mmol) in MeOH (2.0 mL) was added NaOMe (32 mg, 0.59 mmol). The reaction mixture was stirred for 2.5 h, quenched with sat. NH_4Cl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude residue was purified by chromatography on SiO_2 (19:1, hexanes/EtOAc) to give **(+)-173** (62 mg, 82%, >99% ee by HPLC (Chiralcel OD, 99.5:0.5, hexanes/*i*-PrOH) R_t **(-)-173** 17.1 min,[224] **(+)-173** 19.3 min)) as a colorless solid: $[\alpha]_D$ +36.1 (*c* 0.61, $CHCl_3$).

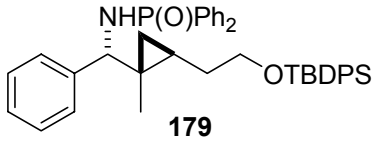


177

***N*-(*R**)-{[(1*R**,2*S**)-2-{2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl}cyclopropyl](phenyl)methyl}-*P*,*P*-diphenylphosphinamide (177)**. **General Protocol E**. To a suspension of Cp_2ZrHCl (9.0 g, 35 mmol) in dry CH_2Cl_2 (60 mL) was added at 0 °C a solution of **125** (11 g, 35 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was warmed to r.t., stirred for 10 min, cooled to -78 °C,

[223] Fife, W. K.; Ranganathan, P.; Zeldin, M. *J. Org. Chem.* **1990**, *55*, 5610.
[224] The peak for the minor enantiomer was inferred from the HPLC trace for (-)-**173**.

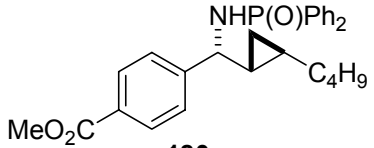
treated with Me_2Zn (18 mL, 35 mmol, 2.0 M in toluene) and warmed to 0 °C. After addition of **19** (3.5 g, 12 mmol), the reaction was heated at reflux for 10 h, cooled to r.t., treated with CH_2I_2 (4.7 mL, 58 mmol), heated at reflux for 4 h and quenched at 0 °C with sat. NH_4Cl. The mixture was filtered through Celite, extracted with EtOAc (3x) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (1:1, hexanes/EtOAc containing 1% v/v Et_3N) to afford **177** (4.0 g, 55%) as a colorless foam: IR (neat) 3188, 3057, 2930, 2857, 1438, 1428, 1189, 1111 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, *J* = 8.7, 5.7 Hz, 1 H), 1.59 (dq, *J* = 13.5, 6.8 Hz, 1 H), 1.39 (dq, *J* = 13.7, 6.8 Hz, 1 H), 1.08 (s, 9 H), 1.08-1.01 (m, 1 H), 0.87-0.76 (m, 1 H), 0.44 (dt, *J* = 8.6, 4.9 Hz, 1 H), 0.30 (dt, *J* = 8.4, 5.1 Hz, 1 H); ^{13}C NMR δ 143.25, 143.18, 135.51, 135.48, 133.95, 132.28, 132.25, 131.89, 131.77, 131.66, 131.53, 129.45, 128.42, 128.20, 128.06, 127.53, 126.95, 126.71, 63.99, 58.61, 36.43, 26.85, 26.57, 26.50, 19.08, 15.53, 10.22; MS (ESI) *m/z* (intensity) 652 ($[M+Na]^+$, 100), 630 ($[M+H]^+$, 10); HRMS (ESI) *m/z* calculated for $C_{40}H_{44}NO_2PSiNa$ (M+Na) 652.2777, found 652.2772.



179

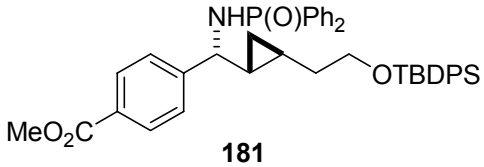
***N*-((*R**)-((1*R**,2*S**)-2-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-1-methylcyclopropyl)(phenyl)-methyl)-P,P-diphenylphosphinamide (179)**. To a suspension of Cp_2ZrHCl (4.6 g, 18 mmol) in dry CH_2Cl_2 (30 mL) was added at 0 °C a solution of **178** (5.7 g, 18 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was warmed to r.t. and stirred for 10 min, cooled to -78 °C, treated with Me_2Zn (8.8 mL, 18 mmol, 2.0 M in toluene) and warmed to 0 °C. After addition of **21** (1.8 g, 5.9 mmol), the mixture was heated at reflux for 10 h, cooled to r.t., treated with CH_2I_2 (2.4 mL, 30 mmol), heated at reflux for 4 h and quenched at 0 °C with sat. NH_4Cl. The solution was filtered through Celite, extracted with EtOAc (3x), and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (1:1, hexanes/EtOAc containing 1% v/v Et_3N) to afford **179** (2.3 g, 61%) as a colorless foam: IR (neat) 3208, 3055, 2930, 2857, 1437, 1185, 1110 cm^{-1}; ^1H NMR δ 7.93-7.86 (m, 2 H), 7.82-7.72 (m, 6 H), 7.55-7.41 (m, 10 H), 7.38-7.26 (m, 7 H), 3.89-3.70 (m, 3 H), 3.35 (dd, *J* = 9.9, 7.0 Hz, 1 H), 1.86-1.75 (m, 1 H), 1.57-1.45 (m, 1 H), 1.12 (s, 9 H), 1.02 (s, 3 H),

0.92 (dd, J = 9.0, 5.0 Hz, 1 H), 0.86-0.76 (m, 1 H), 0.06 (t, J = 5.0 Hz, 1 H); ^{13}C NMR δ 142.23, 142.17, 135.54, 134.12, 134.03, 133.00, 132.97, 132.51, 132.40, 131.90, 131.77, 131.72, 131.69, 131.62, 131.59, 131.25, 129.49, 128.46, 128.29, 128.25, 128.08, 128.04, 127.56, 127.18, 126.86, 64.25, 62.18, 32.26, 26.86, 24.55, 24.48, 19.13, 19.08, 17.25, 15.07; MS (ESI) *m/z* (intensity) 666 ([M+Na]$^+$, 100), 644 ([M+H]$^+$, 33), 428 (29); HRMS (ESI) *m/z* calculated for $C_{41}H_{46}NO_2PSiNa$ (M+Na) 666.2933, found 666.2954.



180

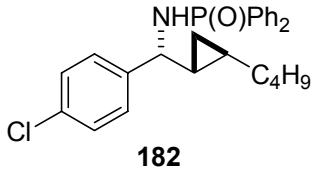
Methyl (*R)-4-((*P*,*P*-diphenylphosphinoylamino)-((1*R**,2*R**)-2-butylcyclopropyl)methyl)-benzoate** (**180**). According to the General Protocol E, Cp_2ZrHCl (0.21 g, 0.83 mmol), **108** (95 μL, 0.83 mmol), Me_2Zn (0.41 mL, 0.83 mmol, 2.0 M in toluene) and **119** (0.10 g, 0.28 mmol) in dry CH_2Cl_2 (2.0 mL) followed by CH_2I_2 (0.11 mL, 1.4 mmol) afforded **180** (88 mg, 69%) as a colorless solid: mp 141.0-143.0 °C (hexanes/EtOAc); IR (KBr) 3172, 2954, 2921, 1720, 1437, 1275, 1181, 1107 cm^{-1}; ^{1}H NMR δ 7.98-7.88 (m, 4 H), 7.76-7.69 (m, 2 H), 7.56-7.69 (m, 4 H), 7.34-7.28 (m, 4 H), 3.93 (s, 3 H), 3.83 (q, J = 8.8 Hz, 1 H), 3.46 (dd, J = 8.4, 5.7 Hz, 1 H), 1.4-1.2 (m, 5 H), 1.17-1.09 (m, 1 H), 1.04-0.95 (m, 1 H), 0.91-0.86 (m, 3 H), 0.80-0.76 (m, 1 H), 0.42 (dt, J = 8.5, 4.8 Hz, 1 H), 0.28 (dt, J = 8.3, 5.0 Hz, 1 H); ^{13}C NMR δ 167.14, 148.81, 148.75, 134.15, 133.12, 132.60, 132.47, 132.17, 132.12, 132.08, 132.04, 131.97, 131.93, 131.39, 129.85, 129.03, 128.8, 128.61, 128.55, 128.38, 127.01, 58.78, 52.28, 33.46, 31.96, 27.11, 27.04, 22.75, 19.20, 14.33, 10.98; MS (EI) *m/z* (intensity) 461 (M$^+$, 13), 364 (100), 256 (37), 218 (17), 201 (91), 164 (9); HRMS (EI) *m/z* calculated for $C_{28}H_{32}NO_3P$ 461.2120, found 461.2134.



181

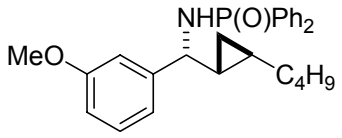
Methyl (*R)-4-((*P*,*P*-diphenylphosphinoylamino)-((1*R**,2*S**)-2-(2-(*tert*-butyldiphenylsilyl)-oxyethyl)cyclopropyl)methyl)benzoate** (**181**). According to the General Protocol E, Cp_2ZrHCl (0.21 g, 0.83 mmol), **125** (0.26 g, 0.83 mmol), Me_2Zn (0.41 mL, 0.83 mmol, 2.0 M in toluene) and **119** (0.10 g, 0.28 mmol) in dry CH_2Cl_2 (2.0 mL) followed by CH_2I_2 (0.11 mL, 1.4 mmol) afforded **181** (0.16 g, 84%) as a colorless foam: IR (neat) 3179, 2930, 2858, 1721, 1435, 1280,

1187, 1109 cm^{-1}; ^1H NMR δ 7.94 (d, *J* = 8.3 Hz, 2 H), 7.87-7.80 (m, 2 H), 7.71-7.67 (m, 1 H), 7.65-7.59 (m, 5 H), 7.44-7.32 (m, 11 H), 7.29-7.23 (m, 4 H), 3.92 (s, 3 H), 3.84-3.68 (m, 3 H), 3.43 (dd, *J* = 8.6, 5.3 Hz, 1 H), 1.51-138 (m, 2 H), 1.02 (s, 9 H), 1.02-0.94 (m, 1 H), 0.84-0.78 (m, 1 H), 0.42 (dt, *J* = 8.6, 5.0 Hz, 1 H), 0.28 (dt, *J* = 8.3, 5.2 Hz, 1 H); ^{13}C NMR δ 167.13, 148.84, 148.78, 135.80, 135.77, 134.17, 134.09, 134.01, 133.11, 132.62, 132.49, 132.32, 132.16, 132.10, 132.07, 132.04, 131.97, 131.94, 131.39, 129.88, 129.82, 129.04, 128.78, 128.62, 128.56, 128.39, 127.88, 127.84, 127.00, 64.30, 58.66, 52.30, 36.67, 27.16, 26.92, 26.85, 19.39, 15.96, 10.70; MS (EI) *m/z* (intensity) 687 (M^+, 0.6), 664 (2), 630 (100), 364 (14), 201 (34), 77 (15); HRMS (EI) *m/z* calculated for $C_{38}H_{37}NO_4PSi$ ($[M-C_4H_9]^+$) 630.2230, found 630.2225.



182

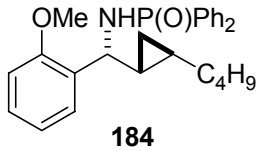
***N*-(*R**)-(((1*R**,2*R**)-2-butylcyclopropyl)(4-chlorophenyl)methyl)-*P*,*P*-diphenylphosphinamide** (**182**). According to the General Protocol E, Cp_2ZrHCl (0.33 g, 0.88 mmol), **108** (0.10 mL, 0.88 mmol), Me_2Zn (0.44 mL, 0.88 mmol, 2.0 M in toluene) and **124** (0.10 g, 0.29 mmol) in dry CH_2Cl_2 (2.0 mL) followed by CH_2I_2 (0.12 mL, 1.5 mmol) afforded **182** (84 mg, 65%) as a colorless solid: mp 147.7-149.5 °C (hexanes/EtOAc); IR (KBr) 3434, 3179, 2920, 1490, 1460, 1436, 1184 cm^{-1}; ^1H NMR δ 7.96-7.89 (m, 2 H), 7.78-7.71 (m, 2 H), 7.57-7.43 (m, 4 H), 7.38-7.19 (m, 6 H), 3.81-3.72 (q, *J* = 8.5 Hz, 1 H), 3.34 (dd, *J* = 8.3, 5.6 Hz, 1 H), 1.4-1.25 (m, 5 H), 1.15-1.08 (m, 1 H), 1.02-0.95 (m, 1 H), 0.92-0.87 (m, 3 H), 0.79, 0.71 (m, 1 H), 0.39 (dt, *J* = 8.5, 4.8 Hz, 1 H), 0.28 (dt, *J* = 8.3, 5.1 Hz, 1 H); ^{13}C NMR δ 142.09, 142.03, 134.09, 133.24, 132.72, 132.44, 132.31, 132.09, 132.96, 131.90, 131.78, 131.75, 131.52, 128.62, 128.43, 128.38, 128.26, 58.39, 33.36, 31.86, 26.90, 26.82, 22.65, 19.09, 14.24, 10.86; MS (EI) *m/z* (intensity) 437 (M^+, 4), 340 (54), 256 (17), 201 (100), 77 (21); HRMS (EI) *m/z* calculated for $C_{26}H_{29}NOPCl$ 437.1675, found 437.1671.



183

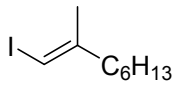
***N*-(*R**)-(((1*R**,2*R**)-2-butylcyclopropyl)(3-methoxyphenyl)methyl)-*P*,*P*-diphenylphosphinamide** (**183**). According to the General Protocol E, Cp_2ZrHCl (0.35 g, 1.3

mmol), **108** (0.15 mL, 1.3 mmol), Me_2Zn (0.67 mL, 1.3 mmol, 2.0 M in toluene) and **121** (0.15 g, 0.45 mmol) in dry CH_2Cl_2 (3.0 mL) followed by CH_2I_2 (0.18 mL, 2.2 mmol) afforded **183** (99 mg, 51%) as a colorless solid: mp 114.5-117.0 °C (hexanes/EtOAc); IR (KBr) 3433, 3164, 2922, 1599, 1461, 1435, 1184 cm^{-1}; ^1H NMR δ 7.91 (ddd, *J* = 11.9, 7.9, 1.4, 2 H), 7.78-7.71 (m, 2 H), 7.51-7.40 (m, 4 H), 7.35-7.27 (m, 2 H), 7.21 (t, *J* = 7.9 Hz, 1 H), 6.86 (d, *J* = 7.7 Hz, 1 H), 6.79-6.75 (m, 2 H), 3.78 (s, 3 H), 3.78-3.69 (m, 1 H), 3.30 (dd, *J* = 8.6, 5.9 Hz, 1 H), 1.35-1.25 (m, 5 H), 1.07-0.94 (m, 2 H), 0.89-0.84 (m, 3 H), 0.78-0.72 (m, 1 H), 0.40 (dt, *J* = 9.4, 4.8 Hz, 1 H), 0.24 (dt, *J* = 10.9, 5.9 Hz, 1 H); ^{13}C NMR δ 159.62, 145.32, 145.24, 134.50, 133.38, 132.80, 132.64, 132.51, 132.16, 132.04, 131.94, 131.90, 131.78, 131.75, 131.66, 129.47, 128.67, 128.50, 128.47, 128.30, 59.10, 55.35, 31.91, 26.97, 26.91, 22.74, 19.10, 14.28, 10.96; MS (EI) *m/z* (intensity) 433 (M^+, 5), 390 (3), 376 (5), 349 (27), 336 (69), 256 (20), 232 (28), 201 (72), 86 (100), 69 (57); HRMS (EI) *m/z* calculated for $C_{27}H_{32}NO_2P$ 433.2171, found 433.2165.



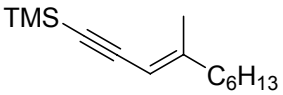
184

***N*-(*R**)-(((1*R**,2*R**)-2-butylcyclopropyl)(2-methoxyphenyl)methyl)-*P*,*P*-diphenylphosphinamide** (**184**). According to the General Protocol E, Cp_2ZrHCl (0.35 g, 1.3 mmol), **108** (0.15 mL, 1.3 mmol), Me_2Zn (0.67 mL, 1.3 mmol, 2.0 M in toluene) and **120** (0.15 g, 0.45 mmol) in dry CH_2Cl_2 (3.0 mL) followed by addition of CH_2I_2 (0.18 mL, 2.2 mmol) afforded **184** (63 mg, 32%) and **129** (0.11 g, 55%) as colorless solids. **184**: mp 155.2-156.0 °C (hexanes/EtOAc); IR (KBr) 3204, 2949, 2923, 1600, 1492, 1436, 1242, 1184 cm^{-1}; ^1H NMR δ 7.90-7.83 (m, 2 H), 7.75-7.68 (m, 2 H), 7.50-7.39 (m, 4 H), 7.33-7.27 (m, 2 H), 7.25-7.19 (m, 1 H), 6.99 (dd, *J* = 7.3, 1.5 Hz, 1 H), 6.89-6.83 (m, 2 H), 4.05-3.98 (m, 1 H), 3.81-3.72 (m, 1 H), 3.74 (s, 3 H), 1.38-1.29 (m, 5 H), 1.21-1.09 (m, 2 H), 0.89 (t, *J* = 6.7 Hz, 3 H), 0.74-0.64 (m, 1 H), 0.30 (dt, *J* = 8.5, 4.7 Hz, 1 H), 0.13 (dt, *J* = 8.4, 5.0 Hz, 1 H); ^{13}C NMR δ 156.84, 132.76, 132.63, 132.19, 132.06, 131.74, 131.71, 131.57, 131.54, 128.56, 128.44, 128.40, 128.34, 128.19, 120.73, 110.97, 57.09, 55.32, 33.67, 31.98, 25.89, 25.83, 22.76, 19.45, 14.37, 10.86; MS (EI) *m/z* (intensity) 433 (M^+, 5), 336 (100), 256 (25), 232 (23), 201 (97); HRMS (EI) *m/z* calculated for $C_{27}H_{32}NO_2P$ 433.2171, found 433.2167.



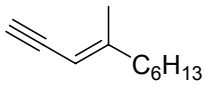
187

1-Iodo-2-methyloct-1-ene (**187**).[225] A cooled (0 °C) solution of Me_3Al (2.2 g, 30 mmol) and Cp_2ZrCl_2 (0.58 g, 2.0 mmol) in dry CH_2Cl_2 (50 mL) was treated dropwise (***Caution: exothermic***)[226] with H_2O (0.27 mL, 15 mmol). The reaction mixture was warmed to room temperature for 20 min, treated at 0 °C with 1-octyne (1.5 mL, 10 mmol), stirred for 30 min and quenched with a solution of I_2 (3.0 g, 12 mmol) in dry THF (15 mL). The solution was stirred for 30 min, poured into saturated K_2CO_3, filtered through Celite and extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexanes) to give **187** (2.1 g, 85%) as a light yellow oil: ^{1}H NMR δ 5.87-5.86 (m, 1 H), 2.20 (t, *J* = 7.2 Hz, 2 H), 1.83 (d, *J* = 0.9 Hz, 3 H), 1.48-1.38 (m, 2 H), 1.34-1.28 (m, 6 H), 0.89 (t, *J* = 7.0 Hz, 3 H).



189

Trimethyl-(4-methyldec-3-en-1-ynyl)silane (189).[227] To a cooled (0 °C) suspension of $(Ph_3P)_4Pd$ (0.46 g, 0.40 mmol), CuI (0.15 g, 0.79 mmol) and **xx** (2.0 g, 7.9 mmol) in freshly distilled *i*-Pr_2NH (20 mL) was added trimethylsilylacetylene (1.7 mL, 12 mmol) and the reaction was stirred for 5 min, quenched with saturated NH_4Cl and extracted with Et_2O (4x). The combined organic layers were washed with 10% HCl (3x), brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on SiO_2 (hexanes) to give xx (1.8 g, 100%) as a colorless oil: ^{1}H NMR δ 5.31-5.30 (m, 1 H), 2.07 (t, *J* = 7.0 Hz, 2 H), 1.91 (d, *J* = 0.9 Hz, 3 H), 1.46-1.36 (m, 2 H), 1.13-1.26 (m, 6 H), 0.89 (t, *J* = 7.0 Hz, 3 H), 0.20 (s, 9 H).

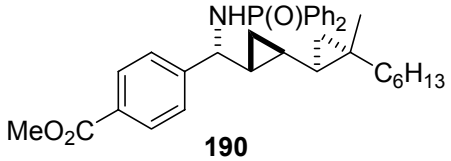


143

4-Methyldec-3-en-1-yne (**143**).[228] To a cooled solution (0 °C) of **189** (4.2 g, 19 mmol) in THF (30 mL) and MeOH (10 mL) was added TBAF (21 mL, 21 mmol, 1.0 M in THF). The reaction

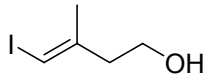
[225] Iwasawa, N.; Maeyama, K. *J. Org. Chem.* **1997**, *62*, 1918.
[226] While under positive N_2 pressure, the flask was equipped with three outlets to reduce the build-up of pressure in the during the H_2O addition. These outlets tend to clog with a colorless solid and need to be replaced periodically.
[227] Zweifel, G.; Leong, W. *J. Am. Chem. Soc.* **1987**, *109*, 6409.
[228] Negishi, E.; Kotora, M.; Xu, C. *J. Org. Chem.* **1997**, *62*, 8957.

mixture was warmed to room temperature, stirred for 2 h, quenched with sat. NH_4Cl and extracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on SiO_2 (petroleum ether, bp 30-60 °C) to give **143** (2.8 g, 96%) as a colorless oil: ^{1}H NMR δ 5.28-5.26 (m, 1 H), 3.01 (dd, *J* = 2.2, 0.4 Hz, 1 H), 2.09 (bt, *J* = 6.9 Hz, 2 H), 1.91 (d, *J* = 0.7 Hz, 3 H), 1.48-1.36 (m, 2 H), 1.34-1.27 (m, 6 H), 0.89 (t, *J* = 6.9 Hz, 3 H).



190

(*R)-(1*R**,2*S**)-4-[*P*,*P*-diphenylphosphinoylamino-(1'*R**,2'*S**)-(2'-hexyl-2'-methylbicyclo-propyl-2-yl)methyl]benzoic acid methyl ester** (**190**). According to the General Protocol E, **143** (62 mg, 0.41 mmol), Cp_2ZrHCl (0.11 g, 0.41 mmol), Me_2Zn (0.21 mL, 0.41 mmol, 2.0 M in toluene) and **119** (50 mg, 0.14 mmol) dry CH_2Cl_2 (1.5 mL) followed by CH_2I_2 (56 μL, 0.69 mmol) afforded **190** (52 mg, 70 %) as a colorless solid: mp 154.0-155.0 °C (hexanes/EtOAc); IR (neat) 3179, 2951, 2922, 2854, 1728, 1437, 1277, 1189, 1122, 1108 cm^{-1}; ^{1}H NMR δ 7.97-7.90 (m, 2 H), 7.90-7.83 (m, 2 H), 7.72-7.65 (m, 2 H), 7.52-7.38 (m, 4 H), 7.31-7.26 (m, 4 H), 3.92 (s, 3 H), 3.87-3.80 (m, 1 H), 3.41 (dd, *J* = 8.8, 5.6 Hz, 1 H), 1.27-1.23 (m, 9 H), 1.17-1.10 (m 1 H), 1.07 (s, 3 H), 1.02-0.94 (m, 1 H), 0.87 (t, *J* = 6.9 Hz, 3 H), 0.65-0.57 (m, 1 H), 0.55-0.49 (m, 1 H), 0.42-0.33 (m, 2 H), 0.18-0.06 (m, 2 H); ^{13}C NMR δ 167.12, 148.51, 148.45, 134.08, 133.03, 132.65, 132.52, 132.39, 132.08, 131.95, 131.91, 131.31, 129.88, 129.81, 129.04, 128.78, 128.61, 128.51, 128.34, 126.99, 58.49, 52.25, 41.32, 32.14, 29.66, 27.37, 27.30, 27.08, 26.94, 22.84, 20.47, 18.99, 18.27, 18.10, 14.28, 11.35; MS (EI) *m/z* (intensity) 543 (M^+, 6), 378 (26), 364 (23), 218 (54), 201 (92), 164 (26), 129 (27), 91 (52), 77 (49); HRMS (EI) *m/z* calculated for $C_{34}H_{42}NO_3P$ 543.2902, found 543.2899.

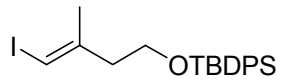


192

(*E*)-4-iodo-3-methylbut-3-en-1-ol (**192**).[229] A solution of Me_3Al (12 g, 0.17 mol) and Cp_2ZrCl_2 (3.3 g, 11 mmol) in dry CH_2Cl_2 (0.15 L) was treated at -78 °C with 3-butyn-1-ol (4.0 g, 57 mmol), warmed to room temperature and stirred for 12 h. The solution was treated at 0 °C with

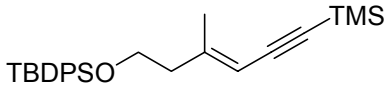
[229] Negishi, E.; Liu, F.; Choueiry, D.; Mohamud, M. M.; Silveira, A.; Reeves, M. *J. Org. Chem.* **1996**, *61*, 8325.

a solution of I_2 (16 g, 63 mmol) in dry THF (50 mL), stirred for 10 min, and poured into ice/sat. $NaHCO_3$.[230] The mixture was acidified with conc. HCl and extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (1:1, hexanes/EtOAc) followed by Kugelrohr distillation (90-110 °C, ~0.10 mm Hg) to give **192** (4.2 g, 35%) as a light yellow oil: ^{1}H NMR δ 6.04-6.03 (m, 1 H), 3.73 (t, *J* = 8.9 Hz, 2 H), 2.49 (td, *J* = 6.3, 1.0 Hz, 1 H), 1.89 (s, 3 H).



193

***tert*-Butyl-(4-iodo-3-methylbut-3-enyloxy)diphenylsilane** (**193**).[231] To a cooled (0 °C) solution of **192** (4.2 g, 20 mmol) was added imidazole (1.9 g, 28 mmol), DMAP (0.24 g, 2.0 mmol) and a solution of TBDPS-Cl (5.6 g, 20 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was warmed to room temperature, stirred for 4 h and filtered through Celite. The filter cake was washed with $CHCl_3$ and the combined organic washings were washed with H_2O, 10% HCl, and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexanes) to give **193** (8.1 g, 91%) as a colorless oil: ^{1}H NMR δ 7.71-7.64 (m, 4 H), 7.47-7.35 (m, 6 H), 5.94-5.93 (m, 1 H), 3.73 (t, *J* = 6.4 Hz, 2 H), 2.44 (td, *J* = 6.4, 0.9 Hz, 2 H), 1.76 (d, *J* = 1.1 Hz, 3 H), 1.05 (s, 9 H).

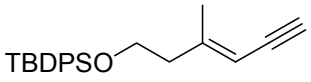


194

(*E*)-*tert*-Butyl-(3-Methyl-6-(trimethylsilanyl)hex-3-en-5-ynyloxy)diphenylsilane (**194**). To a mixture of $Pd(Ph_3P)_4$ (0.90 g, 0.78 mmol) and CuI (0.30 g, 1.6 mmol) in freshly distilled *i*-Pr_2NH (50 mL) at 0 °C was added a solution of **193** (7.0 g, 16 mmol) in *i*-Pr_2NH (20 mL) followed by **188** (3.3 mL, 23 mmol). The reaction mixture was stirred for 10 min, quenched with saturated NH_4Cl and extracted with Et_2O (3x). The combined organic layers washed with H_2O, 10% HCl (2x), brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexanes, then 97:3, hexanes/EtOAc) to give **194** (6.5 g, 99%) as a colorless oil: IR (neat) 3071, 3050, 2958, 2932, 2897, 2858, 2133, 2068, 1473, 1428, 1389, 1250, 1111 cm^{-1}; ^{1}H NMR δ 7.71-7.64 (m, 4 H), 7.46-7.36 (m, 6 H), 5.32 (m, 1 H), 3.73 (t, *J* = 6.7 Hz, 2 H), 2.32 (t, *J* = 6.6

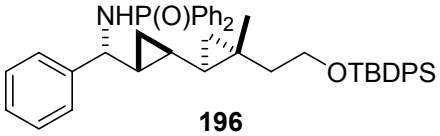
[230] Significant material was lost during the quench due to a broken flask.
[231] Bick, S.; Zimmermann, S.; Meuer, H.; Sheldrick, W. S.; Welzel, P. *Tetrahedron* **1993**, *49*, 2457.

Hz, 2 H), 1.85 (d, J = 1.0 Hz, 2 H), 1.05 (s, 9 H), 0.20 (s, 9 H); ^{13}C NMR δ 150.85, 135.57, 133.72, 129.61, 127.64, 106.79, 103.32, 96.85, 62.39, 41.62, 26.83, 19.76, 19.15, 0.11; MS (EI) *m/z* (intensity) 405 ((M-CH_3)$^+$, 1), 363 (100), 197 (35), 174 (25), 135 (87), 73 (55); HRMS (EI) *m/z* calculated for $C_{25}H_{33}OSi_2$ (M-CH_3) 405.2070, found 405.2085.



195

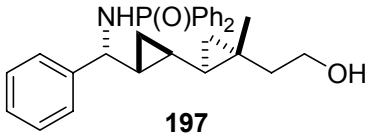
(*E*)-*tert*-Butyl-(3-methyl-hex-3-en-5-ynyloxy)diphenylsilane (**195**). To a vigorously stirred mixture of **194** (1.8 g, 4.2 mmol) in MeOH (17 mL) was added K_2CO_3 (0.64 g, 4.6 mmol). The reaction mixture was stirred for 12 h, quenched with saturated NH_4Cl, diluted with H_2O, and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (95:5, Hexanes/EtOAc) to give **195** (1.5 g, 100%) as a colorless oil: IR (neat) 3308, 3071, 3050, 2932, 2858, 1472, 1428, 1389, 1191, 1111 cm^{-1}; ^{1}H NMR δ 7.67-7.64 (m, 4 H), 7.44-7.37 (m, 6 H), 5.94-5.93 (m, 1 H), 3.73 (t, 2 H, J = 6.4 Hz), 2.44 (td, 2 H, J = 6.4, 1.0 Hz), 1.75 (s, 3 H), 1.05 (s, 9 H); ^{13}C NMR δ 145.04, 135.56, 133.63, 129.63, 127.67, 76.58, 61.81, 42.26, 26.81, 24.02, 19.12; MS (EI) *m/z* (intensity) 291 ((M-C_4H_9)$^+$, 20), 199 (100), 181 (38), 135 (20), 105 (58), 91 (40), 77 (88); HRMS (EI) *m/z* calculated for $C_{25}H_{33}OSi_2$ (M-C_4H_9) 291.1205, found 291.1207.



196

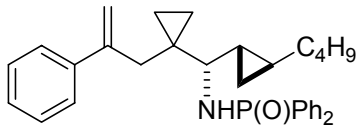
***N*-(*R**)-{(1*R**,2*S**)-[(1'*R**,2'*S**)-2'-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]-2'-methylbicyclopropyl-2-yl]phenylmethyl}-*P*,*P*-diphenylphosphinamide** (**196**). To a suspension of Cp_2ZrHCl (0.51 g, 2.0 mmol) of in CH_2Cl_2 (3.0 mL) was added a solution of **195** (0.69 g, 2.0 mmol) of in dry CH_2Cl_2 (2.0 mL). The reaction was stirred for 10 min, cooled to -78 °C, treated with Me_2Zn (0.98 mL, 2.0 mmol, 2.0 M in toluene), and warmed to 0 °C. After addition of imine (0.20 g, 0.66 mmol), the solution was heated at reflux for 3 h then treated over 75 h with CH_2I_2 (3 x 0.26 mL, 3 x 3.3 mmol) in 24 h intervals. The reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl, filtered through Celite. The aqueous layer was extracted with EtOAc (2x) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered through a pad of Florisil and concentrated. The residue was purified by chromatography on deactivated SiO_2 (1:1,

Hexanes/EtOAc containing 1% Et_3N) to give **196** (0.24 g, 53%) as a colorless foam: IR (neat) 3169, 3056, 2929, 2857, 1590, 1472, 1455, 1437, 1428, 1187, 1110 cm^{-1}; ^1H NMR δ 7.89-7.83 (m, 2 H), 7.73-7.65 (m, 6 H), 7.44-7.37 (m, 10 H), 7.29-7.19 (m, 7 H), 3.83-3.63 (m, 3 H), 3.35 (dd, *J* = 9.0, 5.8 Hz, 1 H), 1.54-1.45 (m. 1 H), 1.39-1.27 (m, 1 H), 1.15-0.93 (m, 13 H), 0.55-0.45 (m, 2 H), 0.38-0.28 (m, 2 H), 0.14-0.05 (m, 2 H); ^{13}C NMR δ 142.95, 142.88, 135.51, 134.19, 133.97, 133.02, 132.48, 132.35, 131.84, 131.72, 131.54, 131.30, 129.46, 128.45, 128.28, 128.17, 128.03, 127.52, 126.94, 126.73, 62.49, 58.39, 43.57, 27.14, 27.07, 26.81, 26.54, 19.05, 18.59, 18.35, 17.85, 17.45, 10.97; MS (EI) *m/z* (intensity) 683 (M^+, 15), 640 (10), 626 (79), 548 (12), 627 (16), 320 (59), 306 (100), 218 (73), 201 (93), 183 (34), 135 (46), 106 (44), 91 (28), 77 (31); HRMS (EI) *m/z* calculated for $C_{44}H_{50}NO_2SiP$ 683.3348, found 683.3316.



197

***N*-(*R**)-{(1*R**,2*S**)-[(1'*R**,2'*S**)-2'-(2-Hydroxyethyl)-2'-methylbicyclopropyl-2-yl]phenyl-methyl}-*P*,*P*-diphenylphosphinamide** (**197**). To a solution of **196** (0.15 g, 0.22 mmol) in THF (1.0 mL) was added AcOH (25 μL, 0.44 mmol) followed by TBAF (0.44 mL, 0.44 mmol, 1.0 M in THF). The reaction mixture was stirred for 12 h, quenched with saturated NH_4Cl and extracted with EtOAc (3x). The combined organic layers were washed with saturated $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (4:1, then 3:2, CH_2Cl_2/Acetone, containing 1% Et_3N) to give **197** (97 mg, 99%) as a colorless foam: IR (neat) 3363, 3059, 2990, 2926, 2872, 1640, 1454, 1438, 1189, 1124, 1110 cm^{-1}; ^1H NMR (500 MHz) δ 7.87 (dd, *J* = 11.7, 7.2 Hz, 2 H), 7.71 (dd, *J* = 11.9, 7.5 Hz, 2 H), 7.52-7.49 (m, 1 H), 7.46-7.39 (m, 3 H), 7.31-7.27 (m, 4 H), 7.24-7.20 (m, 3 H), 3.79-3.68 (m, 3 H), 3.39-3.36 (m, 1 H), 1.72 (bs, 1 H), 1.53 (dt, *J* = 13.6, 6.8 Hz, 1 H), 1.35 (dt, *J* = 14.0, 7.1 Hz, 1 H), 1.20-1.10 (m, 1 H), 1.13 (s, 3 H), 0.68-0.64 (m, 1 H), 0.54-0.51 (m, 1 H), 0.43-0.37 (m, 2 H), 0.29-0.25 (m, 1 H), 0.16 (t, *J* = 4.8 Hz, 1 H); ^{13}C NMR (126 MHz) δ 143.08, 143.04, 133.99, 132.98, 132.63, 132.55, 131.94, 131.86, 131.73, 131.71, 131.63, 128.59, 128.49, 128.38, 128.35, 128.25, 127.15, 126.79, 58.76, 43.67, 27.14, 27.11, 26.60, 18.24, 17.61, 17.53, 11.20; MS (EI) *m/z* (intensity) 445 (M^+, 4), 427 (1), 414 (6), 320 (53), 306 (49), 218 (78), 216 (50), 201 (100), 91 (20), 77 (25); HRMS (EI) *m/z* calculated for $C_{28}H_{32}NO_2P$ 445.2171, found 445.2168.



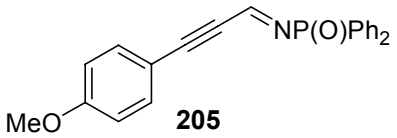
202

***N*-(*S**)-{((1*S**,2*S**)-2-Butylcyclopropyl)-[1-(2-phenylallyl)cyclopropyl]methyl}-*P*,*P*-diphenylphosphinamide (202). Method I. General Protocol F.** To a suspension of Cp_2ZrHCl (0.12 g, 0.46 mmol) in CH_2Cl_2 (2.0 mL) was added **108** (52 μL, 0.46 mmol) and the reaction mixture was stirred for 5 min. The solvent was removed *in vacuo* and the residue was dissolved in dry $Cl(CH_2)_2Cl$ (2.0 mL), cooled to –30 °C, treated with Me_2Zn (0.23 mL, 0.46 mmol, 2.0 M in toluene) and warmed to 0 °C. After addition of **201** (0.10 g, 0.30 mmol), the reaction mixture was stirred at 0 °C for 2 h, cooled to –20 °C and transferred via canula to a mixture of $Zn(CH_2I)_2$ (1.2 mmol) in $Cl(CH_2)_2Cl$ (1.0 mL). The reaction mixture was warmed to 0 °C and stirred for 6 h. The reaction was quenched with saturated NH_4Cl, diluted with EtOAc, filtered through Celite/Florisil (1:1) and the layers were separated. The aqueous layer was extracted with EtOAc (2x) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (3:2, hexanes/EtOAc containing 1% v/v Et_3N) to yield **202** (0.10 g, 68%) as a colorless foam: IR (neat) 3209, 3077, 3057, 2995, 2955, 2924, 2855, 1622, 1592, 1437, 1186, 1123 cm^{-1}; ^1H NMR (C_6D_6) δ 8.11-8.01 (m, 5 H), 7.43-7.39 (m, 3 H), 7.12-7.04 (m, 7 H), 5.28 (d, *J* = 1.6 Hz, 1 H), 5.12 (d, *J* = 0.9 Hz, 1 H), 3.11 (d, *J* = 14.8 Hz, 1 H), 2.98 (dd, *J* = 9.3, 6.7 Hz, 1 H), 2.52 (d, *J* = 14.8 Hz, 1 H), 2.41 (app. q, *J* = 9.2 Hz, 1 H), 1.43-1.30 (m, 6 H), 0.93 (t, *J* = 6.7 Hz, 3 H), 0.78-0.70 (m, 1 H), 0.56-0.46 (m, 2 H), 0.40-0.21 (m, 4 H), 0.15 (dt, *J* = 9.5, 4.9 Hz, 1 H); ^{13}C NMR (C_6D_6) δ 146.24, 142.49, 136.20, 135.98, 134.52, 134.29, 132.74, 132.62, 132.51, 131.35, 131.32, 128.49, 128.43, 127.54, 126.67, 115.06, 61.57, 37.90, 33.97, 32.16, 24.50, 24.43, 23.58, 23.52, 23.04, 18.07, 14.42, 11.97, 10.76, 10.04; MS (EI) *m/z* (intensity) 483 (M^+, 25), 326 (37), 266 (36), 230 (23), 218 (71), 201 (100), 170 (20), 91 (31); HRMS (EI) *m/z* calculated for $C_{32}H_{38}NOP$ 483.2691, found 483.2684.

***N*-(*S**)-{((1*S**,2*S**)-2-Butylcyclopropyl)-[1-(2-phenylallyl)cyclopropyl]methyl}-*P*,*P*-diphenylphosphinamide (202). Method II.** To a suspension of Cp_2ZrHCl (0.24 g, 0.91 mmol) in dry CH_2Cl_2 (2.0 mL) was added **108** (0.10 mL, 0.91 mmol) and the reaction was stirred for 5 min., cooled to -78 °C, treated with Me_2Zn (0.46 mL, 0.91 mmol, 2.0 M in toluene) and warmed to 0 °C. After addition of **201** (0.10 g, 0.30 mmol), the reaction was heated at reflux for 2h,

cooled to 0 °C and added via canula to a mixture of $Zn(CH_2I)_2$ (0.91 mmol) in dry CH_2Cl_2 (1.0 mL + 1.0 mL for flask washing) and the reaction was stirred for 1 h and quenched with sat. NH_4Cl. The mixture was diluted with EtOAc, filtered through Celite/Florisil (1:1) and the layers were separated. The aqueous layer was extracted with EtOAc (2x) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (1:1, hexanes/EtOAc containing 1% v/v Et_3N) to afford **x** (88 mg, 60%) as a light yellow oil.

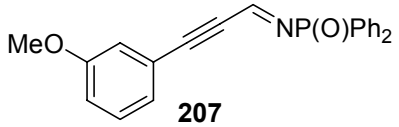
***N*-(*S**)-{((1*S**,2*S**)-2-Butylcyclopropyl)-[1-(2-phenylallyl)cyclopropyl]methyl}-*P*,*P*-diphenylphosphinamide (202). Method III.** To a solution of **228** (77 mg, 0.19 mmol) in dry $Cl(CH_2)_2Cl$ (1.0 mL) was added Me_2Zn (0.14 mL, 0.28 mmol, 2.0 M in toluene) and the reaction was stirred for 1 h, cooled to -20 °C and transferred via canula to a mixture of $Zn(CH_2I)_2$ (0.74 mmol) in dry $Cl(CH_2)_2Cl$ (1.0 mL). The mixture was warmed to 0 °C, stirred for 6 h, quenched with sat. NH_4Cl, diluted with EtOAc and filtered through Celite/Florisil (1:1). The mixture was extracted with EtOAc and the combined organic layers washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (1:1, hexanes/EtOAc containing 1% v/v Et_3N) to afford **202** (65 mg, 72%) as a colorless foam.



205

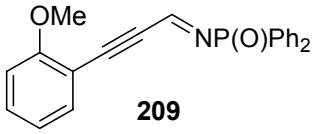
***N*-[3-(4-Methoxyphenyl)prop-2-ynylidene]-*P*,*P*-diphenylphosphinamide (205). General Protocol G.** To a cooled (0 °C) solution of **118** (2.3 g, 11 mmol), DIPEA (5.6 mL, 32 mmol) and **204** (1.9 g, 11 mmol) in dry CH_2Cl_2 (35 mL) was dropwise added a solution of $TiCl_4$ (0.71 mL, 6.5 mmol) in CH_2Cl_2 (5 mL). The reaction was slowly warmed to r.t., stirred for 12 h, poured into dry Et_2O, filtered through Celite/Florisil (1:1) and concentrated. The residue was purified by chromatography on dry SiO_2 (1:1, hexanes/EtOAc containing 1% v/v Et_3N) followed by precipitation from CH_2Cl_2 with excess hexanes to yield **205** (2.1 g, 49%) as a light yellow solid: mp 128.8-130.5 °C (hexanes/CH_2Cl_2); IR (KBr) 3053, 3019, 2191, 1579, 1567, 1512, 1437, 1304, 1266, 1210, 1189, 1180, 1125 cm^{-1}; ^1H NMR δ 8.72 (d, J = 31.3 Hz, 1 H), 7.94-7.87 (m, 4 H), 7.59-7.44 (m, 8 H), 6.93-6.88 (m, 2 H), 3.85 (s, 3 H); ^{13}C NMR δ 161.64, 158.18, 158.11, 134.91, 132.75, 131.93, 131.89, 131.57, 131.44, 131.07, 128.52, 128.35, 114.28, 112.11, 102.07, 88.34, 87.86, 55.30; MS (EI) *m/z* (intensity) 360 ($[M+H]^+$, 22), 359 (M^+, 67), 358 (64),

208 (32), 202 (100), 201 (72), 160 (27), 155 (36), 125 (21); HRMS (EI) *m/z* calculated for $C_{22}H_{18}NO_2P$ 359.1075, found 359.1058.



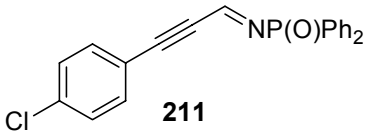
207

***N*-[3-(3-Methoxyphenyl)prop-2-ynylidene]-*P*,*P*-diphenylphosphinamide (207).** According to the General Protocol G, **118** (2.0 g, 9.0 mmol), DIPEA (4.7 mL, 27 mmol), **206** (1.4 g, 9.0 mmol), $TiCl_4$ (0.60 mL, 5.4 mmol), and CH_2Cl_2 (50 mL) afforded **207** (0.70 g, 21%) as an orange/brown solid: mp 109.2-112.5 °C (hexanes/CH_2Cl_2); IR (KBr) 3144, 3055, 3007, 2965, 2934, 2205, 1656, 1589, 1491, 1465, 1436, 1420, 1322, 1298, 1207, 1125, 1109 cm^{-1}; ^1H NMR δ 8.74 (d, *J* = 31.2 Hz, 1 H), 7.9-7.88 (m, 4 H), 7.53-7.44 (m, 6 H), 7.30 (t, J = 7.8 Hz, 1 H), 7.21 (dt, *J* = 7.6, 1.2 Hz, 1 H), 7.13-7.12 (m, 1 H), 7.01 (ddd, *J* = 8.2, 2.6, 1.1 Hz, 1 H), 3.81 (s, 3 H); ^{13}C NMR δ 159.42, 158.13, 158.06, 132.74, 132.03, 132.00, 131.68, 131.55, 131.06, 129.68, 128.60, 128.43, 125.45, 121.36, 117.62, 117.31, 100.52, 88.06, 87.58, 55.33; MS (EI) *m/z* (intensity) 360 ($[M+H]^+$, 23), 359 (M^+, 77), 358 (91), 208 (40), 202 (94), 201 (100), 155 (28); HRMS (EI) *m/z* calculated for $C_{22}H_{18}NO_2P$ 359.1075, found 359.1059.



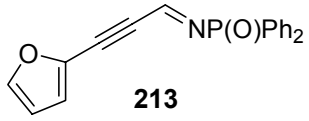
209

***N*-[3-(2-Methoxyphenyl)-prop-2-ynylidene]-*P*,*P*-diphenylphosphinamide (209).** According to the General Protocol G, **118** (2.7 g, 12 mmol), DIPEA (6.5 mL, 38 mmol), **208** (2.0 g, 12 mmol), $TiCl_4$ (0.82 mL, 7.5 mmol), and CH_2Cl_2 (85 mL) afforded **209** (2.2 g, 50%) as a yellow/orange foam: IR (neat) 3058, 2945, 2838, 2194, 1656, 1584, 1490, 1464, 1438, 1271, 1206, 1164, 1124, 1107 cm^{-1}; ^1H NMR δ 8.78 (d, *J* = 31.3 Hz, 1 H), 7.98-7.88 (m, 4 H), 7.57-7.40 (m, 8 H), 6.96 (t, *J* = 7.5 Hz, 1 H), 6.91 (d, *J* = 8.5 Hz, 1 H), 3.90 (s, 3 H); ^{13}C NMR δ 164.44, 158.62, 158.55, 135.04, 132.95, 132.78, 132.21, 132.17, 131.90, 131.78, 131.27, 128.78, 128.61, 120.79, 111.00, 109.82, 98.27, 92.66, 92.17, 55.99; MS (EI) *m/z* (intensity) 360 ($[M+H]^+$, 15), 359 (M^+, 62), 201 (100), 185 (21), 158 (60), 105 (59), 94 (22), 91 (35); HRMS (EI) *m/z* calculated for $C_{22}H_{18}NO_2P$ 359.1075 found 359.1085.



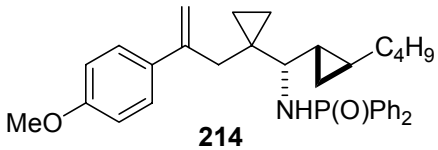
211

***N*-[3-(4-Chlorophenyl)prop-2-ynylidene]-*P*,*P*-diphenylphosphinamide (211).** According to the General Protocol G, **118** (0.52 g, 3.2 mmol), DIPEA (1.7 mL, 9.6 mmol), **210** (0.52 g, 3.2 mmol), $TiCl_4$ (0.21 mL, 1.9 mmol), and CH_2Cl_2 (20 mL) afforded **211** (0.42 g, 36%) as an orange/brown foam: IR (neat) 3131, 3056, 2197, 1658, 1582, 1488, 1437, 1193, 1124 cm^{-1}; ^1H NMR δ 8.70 (d, *J* = 31.2 Hz, 1 H), 7.92-7.85 (m, 4 H), 7.51-7.39 (m, 8 H), 7.32 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR δ 157.69, 157.62, 136.99, 133.90, 132.36, 132.00, 131.96, 131.49, 131.36, 130.68, 128.92, 128.51, 128.34, 118.66, 98.92, 98.89, 88.91, 88.43; MS (EI) *m/z* (intensity) 364 ($[M+H]^+$, 20), 363 (M^+, 40), 212 (27), 202 (71), 201 (100); HRMS (EI) *m/z* calculated for $C_{21}H_{15}NOPCl$ 363.0580, found 363.0575.



213

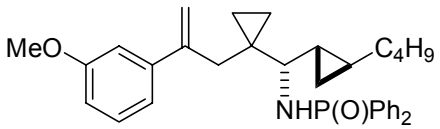
***N*-(3-Furan-2-ylprop-2-ynylidene)-*P*,*P*-diphenylphosphinamide (213).** According to the General Protocol G, **118** (2.7 g, 12 mmol), DIPEA (6.5 mL, 38 mmol), **212** (1.5 g, 12 mmol), $TiCl_4$ (0.81 mL, 7.5 mmol), and CH_2Cl_2 (85 mL) afforded **213** (0.96 g, 24%) as a crude orange/brown oil. This material was used without purification for the following reaction: ^1H NMR (C_6D_6) δ 8.75 (d, *J* = 31.1 Hz, 1 H), 8.09-8.01 (m, 4 H), 7.11-7.01 (m, 6 H), 7.30 (d, *J* = 1.6 Hz, 1 H), 6.35 (d, *J* = 3.5 Hz, 1 H), 5.75 (dd, *J* = 3.5, 1.7 Hz, 1 H); ^{13}C NMR (C_6D_6) δ 156.73, 156.66, 146.78, 132.09, 132.05, 131.98, 131.93, 131.88, 131.84, 128.75, 128.59, 121.28, 111.96, 94.72, 94.23, 89.62; MS (EI) *m/z* (intensity) 320 ($[M+H]^+$, 26), 319 (M^+, 55), 217 (48), 202 (71), 201 (100), 91 (54); HRMS (EI) *m/z* calculated for $C_{19}H_{14}NO_2P$ 319.0762, found 319.0755.



214

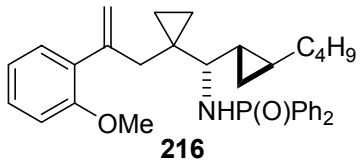
***N*-(*S**)-(((1*S**,2*S**)-2-Butylcyclopropyl)(1-(2-(4-methoxyphenyl)allyl)cyclopropyl)methyl)-*P*,*P*-diphenylphosphinamide (214).** According to the General Protocol F, Cp_2ZrHCl (0.16 g, 0.63 mmol), **108** (72 μL, 0.63 mmol), Me_2Zn (0.31 mL, 0.63 mmol, 2.0 M in toluene), **205** (0.15

g, 0.42 mmol), CH_2I_2 (0.27 mL, 3.3 mmol) and Et_2Zn (0.21 g, 1.7 mmol) in $Cl(CH_2)_2Cl$ (5.0 mL) afforded **214** (0.11 g, 50 %) as a colorless foam: IR (neat) 3230, 3059, 2998, 2955, 2926, 2854, 1674, 1601, 1512, 1438, 1250, 1180, 1123, 1110 cm^{-1}; ^1H NMR (C_6D_6) δ 8.11-7.98 (m, 4 H), 7.43-7.38 (m, 2 H), 7.13-7.05 (m, 6 H), 6.80-6.75 (m, 2 H), 5.28 (d, *J* = 1.7 Hz, 1 H), 5.07 (bs, 1 H), 3.31 (s, 3 H), 3.15 (d, *J* = 14.8 Hz, 1 H), 3.12-3.06 (m, 1 H), 2.56 (d, *J* = 14.6 Hz, 1 H), 2.40 (app. q, *J* = 9.1 Hz, 1 H), 1.39-1.33 (m, 6 H), 0.93 (t, *J* = 6.8 Hz, 3 H), 0.76-0.71 (m, 1 H), 0.60-0.53 (m, 2 H), 0.46-0.37 (m, 2 H), 0.34-0.29 (m, 2 H), 0.18 (dt, *J* = 8.3, 4.9 Hz, 1 H); ^{13}C NMR (C_6D_6) δ 159.67, 145.60, 136.27, 136.11, 134.80, 134.59, 134.42, 132.78, 132.70, 132.66, 132.58, 131.37, 128.47, 127.84, 113.99, 113.49, 61.94, 54.75, 37.95, 34.01, 32.21, 24.58, 24.51, 23.63, 23.56, 23.08, 18.16, 14.44, 11.96, 10.92, 10.21; MS (EI) *m/z* (intensity) 514 ($[M+H]^+$, 4), 513 (M^+, 11), 326 (45), 296 (63), 239 (33), 218 (60), 201 (100), 121 (35), 77 (39); HRMS (EI) *m/z* calculated for $C_{33}H_{40}NO_2P$ 513.2797, found 513.2788.



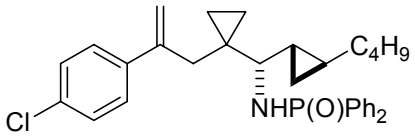
215

***N*-(*S**)-(((1*S**,2*S**)-2-Butylcyclopropyl)(1-(2-(3-methoxyphenyl)allyl)cyclopropyl)methyl)-*P*,*P*-diphenylphosphinamide (215).** According to the General Protocol F, Cp_2ZrHCl (0.16 g, 0.63 mmol), **108** (72 μL, 0.63 mmol), Me_2Zn (0.31 mL, 0.63 mmol, 2.0 M in toluene), **207** (0.15 g, 0.42 mmol), CH_2I_2 (0.27 mL, 3.3 mmol) and Et_2Zn (0.21 g, 1.7 mmol) in $Cl(CH_2)_2Cl$ (5.0 mL) afforded **215** (0.11 g, 50%) as a colorless foam: IR (neat) 3213, 3057, 2996, 2955, 2925, 2855, 1597, 1576, 1488, 1437, 1287, 1186, 1123 cm^{-1}; ^1H NMR (C_6D_6) δ 8.12-8.01 (m, 4 H), 7.22-7.21 (m, 1 H), 7.12-7.04 (m, 8 H), 6.71 (dt, *J* = 9.2, 2.6 Hz, 1 H), 5.33 (d, *J* = 1.6 Hz, 1 H), 5.12 (s, 1 H), 3.38 (s, 3 H), 3.13 (d, *J* = 14.8 Hz, 1 H), 2.94 (dd, *J* = 9.4, 6.9 Hz, 1 H), 2.52 (d, *J* = 14.7 Hz, 1 H), 2.41 (app. q, *J* = 9.2 Hz, 1 H), 1.37-1.23 (m, 7 H), 0.95-0.88 (m, 1H), 0.93 (t, *J* = 6.6 Hz, 1 H), 0.76-0.72 (m, 1 H), 0.53-0..44 (m, 2 H), 0.42-0.35 (m, 2 H), 0.32-0.24 (m, 2 H), 0.17 (dt, *J* = 13.1, 5.0 Hz, 1 H); ^{13}C NMR (C_6D_6) δ 160.25, 146.24, 144.13, 136.18, 135.98, 134.50, 134.29, 132.81, 132.66, 132.53, 131.37, 129.51, 128.47, 119.19, 115.26, 112.98, 112.85, 61.61, 54.84, 37.93, 34.03, 32.20, 24.57, 24.50, 23.64, 23.57, 23.08, 18.08, 14.44, 12.06, 10.81, 10.05; MS (EI) *m/z* (intensity) 513 (M^+, 2), 416 (3), 296 (28), 218 (47), 216 (63), 201 (100); HRMS (EI) *m/z* calculated for $C_{33}H_{40}NO_2P$ 513.2797, found 513.2813.



216

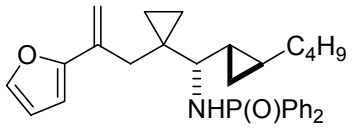
***N*-(*S**)-(((1*S**,2*S**)-2-Butylcyclopropyl)(1-(2-(2-methoxyphenyl)allyl)cyclopropyl)methyl)-*P*,*P*-diphenylphosphinamide (216).** According to the General Protocol F, Cp_2ZrHCl (0.11 g, 0.42 mmol), **108** (48 μL, 0.42 mmol), Me_2Zn (0.21 mL, 0.42 mmol, 2.0 M in toluene), **209** (0.10 g, 0.28 mmol), CH_2I_2 (0.18 mL, 2.2 mmol) and Et_2Zn (0.14 g, 1.1 mmol) in $Cl(CH_2)_2Cl$ (3.5 mL) afforded **216** (76 mg, 53%) as a colorless foam: IR (neat) 3221, 3057, 2996, 2955, 2924, 2854, 1626, 1597, 1576, 1490, 1464, 1437, 1241, 1192, 1122 cm^{-1}; ^1H NMR (C_6D_6) δ 8.12-7.99 (m, 4 H), 7.13-7.01 (m, 8 H), 6.77 (dt, *J* = 7.4, 0.9 Hz, 1 H), 6.48 (d, *J* = 8.2 Hz, 1 H), 5.45 (s, 1 H), 5.19 (d, *J* = 2.2 Hz, 1 H), 3.29 (d, *J* = 15.2 Hz, 1 H), 3.26-3.21 (m, 1 H), 3.21 (s, 3 H), 2.57 (d, *J* = 15.1 Hz, 1 H), 2.47 (app. q, *J* = 9.1 Hz, 1 H), 1.54-1.42 (m, 1 H), 1.39-1.30 (m, 4 H), 0.92 (t, *J* = 6.8 Hz, 3 H), 0.81-0.72 (m, 2 H), 0.65-0.54 (m, 2 H), 0.47-0.37 (m, 2 H), 0.36-0.22 (m, 2 H), 0.12 (dt, *J* = 8.3, 4.7 Hz, 1 H); ^{13}C NMR (C_6D_6) δ 156.84, 146.90, 136.74, 136.19, 135.06, 134.51, 133.10, 132.84, 132.72, 132.68, 132.56, 131.30, 131.26, 131.22, 130.43, 120.89, 117.54, 111.06, 61.16, 54.79, 40.68, 33.99, 32.15, 25.04, 24.96, 23.83, 23.78, 23.07, 18.23, 14.44, 11.90, 11.35, 10.98; MS (EI) *m/z* (intensity) 513 (M^+, 15), 326 (40), 296 (63), 239 (26), 218 (67), 201 (100), 121 (34), 91 (28); HRMS (EI) *m/z* calculated for $C_{33}H_{40}NO_2P$ 513.2797, found 513.2799.



217

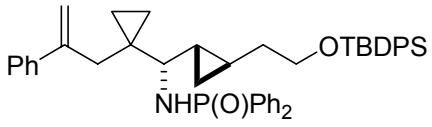
***N*-(*S**)-(((1*S**,2*S**)-2-Butylcyclopropyl)(1-(2-(4-chlorophenyl)allyl)cyclopropyl)methyl)-*P*,*P*-diphenylphosphinamide (217).** According to the General Protocol F, Cp_2ZrHCl (0.17 g, 0.66 mmol), **108** (76 μL, 0.66 mmol), Me_2Zn (0.33 mL, 0.66 mmol, 2.0 M in toluene), **207** (0.16 g, 0.44 mmol), CH_2I_2 (0.28 mL, 3.5 mmol) and Et_2Zn (0.22 g, 1.8 mmol) in $Cl(CH_2)_2Cl$ (5.0 mL) afforded **217** (0.13 g, 58%) as a colorless foam: IR (neat) 3211, 3058, 2995, 2955, 2924, 2855, 1493, 1437, 1185, 1123, 1108 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.93-7.83 (m, 4 H), 7.53-7.40 (m, 8 H), 7.33-7.27 (m, 2 H), 5.33 (d, *J* = 1.5 Hz, 1 H), 5.13 (d, *J* = 1.3 Hz, 1 H), 4.29 (t, *J* = 9.9 Hz, 1 H), 3.14 (d, *J* = 14.9 Hz, 1 H), 2.71 (d, *J* = 14.9 Hz, 1 H), 2.37 (app. q, *J* = 9.4 Hz, 1 H), 1.33-1.24 (m 6 H), 0.85 (t, *J* = 6.8 Hz, 3 H), 0.79-0.71 (m, 1 H), 0.63-0.49 (m, 3 H), 0.37 (dt, *J* = 8.3,

4.6 Hz, 1 H), 0.27-0.15 (m, 3 H); ^{13}C NMR (acetone-d_6) δ 145.53, 141.81, 137.12, 137.00, 135.44, 135.33, 133.37, 132.99, 132.96, 132.87, 132.83, 132.02, 131.99, 129.00, 128.82, 115.67, 61.40, 37.97, 34.38, 32.47, 24.77, 24.71, 23.85, 23.78, 23.30, 18.18, 14.42, 12.32, 10.46, 9.87; MS (EI) *m/z* (intensity) 518 ([M+H]$^+$, 2), 517 (M$^+$, 5), 218 (44), 201 (100), 77 (24); HRMS (EI) *m/z* calculated for $C_{32}H_{37}NOPCl$ 517.2301, found 517.2306.



218

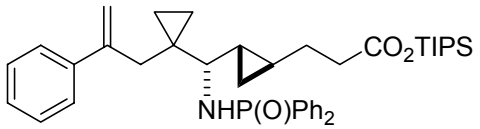
***N*-{(*S**)-((1*S**,2*S**)-2-Butylcyclopropyl)-[1-(2-furan-2-yl-allyl)cyclopropyl]methyl}-*P*,*P*-diphenylphosphinamide (218).** According to the General Protocol F, Cp_2ZrHCl (0.12 g, 0.47 mmol), **108** (54 μL, 0.47 mmol), Me_2Zn (0.24 mL, 0.47 mmol, 2.0 M in toluene), **217** (0.10 g, 0.31 mmol), CH_2I_2 (0.20 mL, 2.5 mmol) and Et_2Zn (0.15 g, 1.2 mmol) in $Cl(CH_2)_2Cl$ (3.0 mL) afforded **218** (69 mg, 47%) as a colorless foam: IR (KBr) 3198, 3055, 2922, 1625, 1591, 1438, 1186, 1123, 1111 cm^{-1}; ^{1}H NMR (C_6D_6) δ 8.12-8.04 (m, 3 H), 7.12-7.04 (m, 7 H), 7.00-6.99 (m, 1 H), 6.51 (d, *J* = 2.9 Hz, 1 H), 6.13 (dd, *J* = 3.3, 1.8 Hz, 1 H), 5.70 (d, *J* = 1.5 Hz, 1 H), 5.00 (d, *J* = 1.1 Hz, 1 H), 2.98-2.93 (m, 1 H), 2.93 (d, *J* = 14.6 Hz, 1 H), 2.48 (d, *J* = 14.4 Hz, 1 H), 2.32 (app. q, *J* = 8.8 Hz, 1 H), 1.39-1.33 (m, 6 H), 0.93 (t, *J* = 6.7 Hz, 3 H), 0.75-0.74 (m, 1 H), 0.56-0.47 (m, 2 H), 0.45-0.28 (m, 4 H), 0.17 (dt, *J* = 8.3, 4.9 Hz, 1 H); ^{13}C NMR (C_6D_6) δ 155.78, 141.93, 136.03, 135.90, 135.04, 134.34, 134.21, 132.72, 132.60, 131.45, 131.41, 128.21, 112.10, 111.50, 107.20, 62.28, 62.25, 35.24, 33.96, 32.24, 24.10, 24.03, 23.58, 23.51, 23.07, 18.09, 14.43, 11.97, 10.71, 9.85; MS (EI) *m/z* (intensity) 474 ([M+H]$^+$, 5), 473 (M$^+$, 16), 326 (23), 256 (18), 218 (43), 201 (100); HRMS (EI) *m/z* calculated for $C_{30}H_{36}NO_2P$ 473.2484, found 473.2482.



219

***N*-(*S**)-{{(1*S**,2*R**)-2-[2-(*tert*-Butyldiphenylsilanyloxy)ethyl]cyclopropyl}-[1-(2-phenylallyl)-cyclopropyl]methyl}-*P*,*P*-diphenylphosphinamide (219)**. To a suspension of Cp_2ZrHCl (0.35 g, 1.4 mmol) in dry CH_2Cl_2 (4.0 mL) was added a solution of **125** (0.42 g, 1.4 mmol) in dry CH_2Cl_2 (2.0 mL). The reaction mixture was stirred for 5 min, solvent was removed *in vacuo* and the residue was dissolved in $Cl(CH_2)_2Cl$ (4.0 mL), cooled to –30 °C, treated with Me_2Zn (0.69

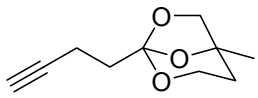
mL, 1.4 mmol, 2.0 M in toluene) and warmed to 0 °C. After addition of **201** (0.30 g, 0.91 mmol), the mixture was stirred at 0 °C for 2 h, cooled to –30 °C and treated with a solution of $Zn(CH_2I)_2$•DME (3.6 mmol) in $Cl(CH_2)_2Cl$ (3.0 mL). The reaction mixture was warmed to 0 °C, stirred for 3 h, quenched with saturated NH_4Cl, diluted with EtOAc, and filtered through Celite/Florisil (1:1). The aqueous layer was extracted with EtOAc (2x) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (3:2, hexanes/EtOAc containing 1% v/v Et_3N) to yield **219** (0.36 g, 55%) as a colorless foam: IR (neat) 3208, 3054, 2929, 2857, 1437, 1428, 1185, 1109 cm^{-1}; ^1H NMR (C_6D_6) δ 8.09-7.99 (m, 4 H), 7.83-7.79 (m, 4 H), 7.41-7.38 (m, 2 H), 7.27-7.22 (m, 8 H), 7.10-7.00 (m, 7 H), 5.26 (d, *J* = 1.5 Hz, 1 H), 5.08 (bs, 1 H), 3.90-3.76 (m, 2 H), 3.09 (d, *J* = 14.9 Hz, 1 H), 2.88 (dd, *J* = 9.6, 6.1 Hz, 1 H), 2.48 (d, *J* = 14.8 Hz, 1 H), 2.37 (app. q, *J* = 9.2 Hz, 1 H), 1.89-1.78 (m, 1 H), 1.29-1.13 (m, 1 H), 1.20 (s, 9 H), 0.80-0.72 (m, 1 H), 0.53-0.43 (m, 2 H), 0.39-0.31 (m, 2 H), 0.29-0.20 (m, 2 H), 0.16-0.10 (m, 1 H); ^{13}C NMR (C_6D_6) δ 146.30, 142.51, 136.01, 135.85, 135.52, 134.16, 132.78, 132.66, 132.61, 132.48, 131.37, 129.88, 126.70, 115.06, 64.51, 61.33, 38.02, 37.36, 27.18, 24.53, 23.40, 23.34, 19.43, 14.75, 11.54, 10.78, 10.08; MS (ESI) *m/z* (rel. intensity) 710 ($[M+H]^+$, 100); HRMS (ESI) *m/z* calculated for $C_{46}H_{53}NO_2PSi$ (M+H) 710.3583, found 710.3563.



220

(*S)-3-((1*S**,2*S**)-2-{*P*,*P*-Diphenylphosphinoylamino-[1-(2-phenylallyl)cyclopropyl]-methyl}cyclopropyl)propionic acid triisopropylsilyl ester (220).** According to the General Protocol F, Cp_2ZrHCl (0.12 g, 0.46 mmol), **139** (0.12 g, 0.46 mmol), Me_2Zn (0.23 mL, 0.46 mmol, 2.0 M in toluene), **201** (0.10 g, 0.30 mmol), CH_2I_2 (0.20 mL, 2.4 mmol) and Et_2Zn (0.15 g, 1.2 mmol) in $Cl(CH_2)_2Cl$ (3.0 mL) afforded **220** (0.11 g, 55%) as a colorless foam: IR (neat) 3207, 3057, 2945, 2867, 1716, 1622, 1464, 1438, 1269, 1186, 1123 cm^{-1}; ^1H NMR (C_6D_6) δ 8.12-7.97 (m, 5 H), 7.40-7.35 (m, 3 H), 7.13-7.02 (m, 7 H), 5.25 (d, *J* = 1.6 Hz, 1 H), 5.06 (d, *J* = 1.1 Hz, 1 H), 3.06 (dd, *J* = 9.6, 6.2 Hz, 1 H), 3.00 (d, *J* = 15.2 Hz, 1 H), 2.51 (d, *J* = 14.0 Hz, 1 H), 2.52-2.34 (m, 2 H), 2.36 (app q, *J* = 9.2 Hz, 1 H), 1.82-1.68 (m, 1 H), 1.45-1.24 (m, 4 H), 1.12 (d, *J* = 6.8 Hz, 18 H), 0.92-0.82 (m, 1 H), 0.57-0.44 (m, 2 H), 0.36-0.21 (m, 4 H), 0.14 (dt, *J* = 8.4, 4.9 Hz, 1 H); ^{13}C NMR (C_6D_6) δ 173.63, 146.10, 142.50, 136.10, 135.60, 134.42, 133.91,

132.85, 132.73, 132.66, 132.54, 131.45, 129.33, 126.67, 115.08, 61.27, 38.00, 35.88, 30.17, 29.81, 24.44, 24.36, 23.85, 23.79, 18.06, 17.70, 12.28, 11.93, 10.57, 10.01; MS (EI) *m/z* (intensity) 655 (M^+, 55), 612 (89), 498 (17), 454 (13), 438 (20), 330 (49), 218 (90), 201 (100); HRMS (EI) *m/z* calculated for $C_{40}H_{54}NO_3PSi$ 655.3611, found 655.3616.

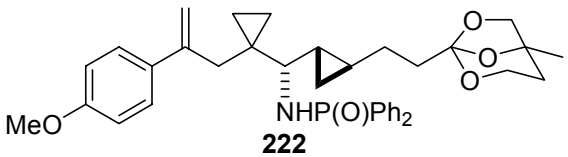


221

1-But-3-ynyl-5-methyl-2,7,8-trioxabicyclo[3.2.1]octane (221). To a solution of 4-pentynoic acid (1.0 g, 10 mmol) in dry CH_2Cl_2 (27 mL) and DMF (3.0 mL) was added DCC (2.1 g, 10 mmol), DMAP (84 mg, 0.68 mmol) and 2-(2-methyloxiranyl)ethanol[232] (0.70 g, 0.68 mmol) and the reaction mixture was stirred for 6 h, filtered through Celite, washed with 10% HCl and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (4:1, hexanes/EtOAc) to give 2-(2-methyloxiran-2-yl)ethyl pent-4-ynoate (0.92 g, 74%): IR (neat) 3284, 2967, 1736, 1423, 1391, 1167 cm^{-1}; ^1H NMR δ 4.31-4.15 (m, 2 H), 2.67-2.47 (m, 3 H), 2.66 (d, *J* = 4.7 Hz, 1 H), 2.61 (d, *J* = 4.8 Hz, 1 H), 2.02-1.82 (m, 2 H), 1.98 (t, *J* = 2.1 Hz, 1 H), 1.63-1.60 (m, 1 H), 1.37 (s, 3H); ^{13}C NMR δ 171.44, 82.26, 69.01, 61.06, 54.72, 53.44, 35.41, 33.18, 21.06, 14.18; MS (EI) *m/z* (intensity) 182 (M^+, 3), 181 (5), 152 (96), 137 (36), 124 (54), 111 (92), 109 (100); HRMS (EI) *m/z* calculated for $C_9H_{12}O_2$ (M-CH_2O) 152.0837 found 152.0835. To a solution of 2-(2-methyloxiran-2-yl)ethyl pent-4-ynoate (0.50 g, 2.7 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C was added Cp_2ZrCl_2 (80 mg, 0.27 mmol) and $AgClO_4$ (6.0 mg, 29 μmol). The reaction was stirred for 4 h, filtered through a pad of Florisil, washed with sat. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on dry SiO_2 (7:3, hexanes/EtOAc containing 1% v/v Et_3N) to yield **221** as a colorless oil which solidified on standing (0.46 g, 91%): IR (neat) 3289, 2976, 2953, 2888, 1447, 1392, 1305, 1266, 1203, 1190, 1143, 1074, 1055 cm^{-1}; ^1H NMR (C_6D_6) δ 3.76 (ddd, *J* = 12.5, 11.4, 4.3 Hz, 1 H), 3.50 (dd, *J* = 11.3, 6.7 Hz, 1 H), 3.41 (d, *J* = 7.0 Hz, 1 H), 3.09 (dd, *J* = 7.0, 2.2 Hz, 1 H), 2.63-2.57 (m, 2 H), 2.41-2.35 (m, 2 H), 1.71 (t, *J* = 2.7 Hz, 1 H), 1.57 (ddt, *J* = 12.8, 6.7, 2.2 Hz, 1 H), 0.88 (s, 3 H), 0.60 (dd, *J* = 13.1, 4.2 Hz, 1 H); ^{13}C NMR (C_6D_6) δ 120.02, 83.92, 78.50, 73.60, 68.72, 59.04, 35.52, 33.69, 21.75, 13.57; MS (EI) *m/z* (intensity) 183

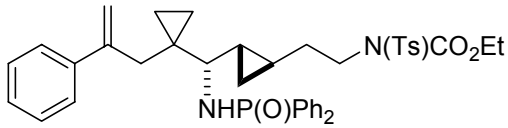
[232] Bats, J.-P.; Moulines, J.; Picard, P.; Leclercq, D.; *Tetrahedron* **1982**, *38*, 2139.

([M+H]$^+$, 4), 181 (2), 152 (30), 109 (32), 99 (44), 84 (51), 81 (100); HRMS (EI) *m/z* calculated for $C_9H_{12}O_2$ (M-CH_2O) 152.0837 found 152.0840.



222

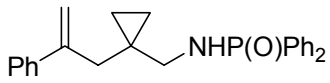
***N*-(*S**)-((1-(2-(4-Methoxyphenyl)allyl)cyclopropyl)-(1*S**,2*S**)-(2-(2-(5-methyl-2,7,8-trioxa-bicyclo[3.2.1]octan-1-yl)ethyl)cyclopropyl)methyl)-*P*,*P*-diphenylphosphinamide (222).** According to the General Protocol F, Cp_2ZrHCl (0.11 g, 0.42 mmol), **221** (76 mg, 0.42 mmol), Me_2Zn (0.21 mL, 0.42 mmol, 2.0 M in toluene), **205** (0.10 g, 0.28 mmol), CH_2I_2 (0.18 mL, 2.2 mmol) and Et_2Zn (0.14 g, 1.1 mmol) in $Cl(CH_2)_2Cl$ (3.0 mL) afforded **222** (75 mg, 44%) as a colorless oil: IR (neat) 3218, 3058, 2933, 2885, 1608, 1513, 1438, 1248, 1189, 1123, 1109 cm^{-1}; ^{1}H NMR (C_6D_6) δ 8.15-8.08 (m, 6 H), 7.44 (d, *J* = 8.7 Hz, 2 H), 7.15-7.08 (m, 4 H), 6.79 (d, *J* = 8.7 Hz, 2 H), 5.27 (s, 1 H), 5.05 (s, 1 H), 3.88 (dt, *J* = 11.7, 4.1 Hz, 1 H), 3.62 (dd, *J* = 11.2, 6.7 Hz, 1 H), 3.52 (dd, *J* = 6.7, 2.3 Hz, 1 H), 3.32 (s, 3 H), 3.31-3.19 (m, 2 H), 3.11 (d, *J* = 14.7 Hz, 1 H), 2.57 (d, *J* = 14.7 Hz, 1 H), 2.39-2.25 (m, 4 H), 1.77-1.57 (m, 3 H), 0.99 (s, 3 H), 0.81-0.64 (m, 3 H), 0.58-0.52 (m, 1 H), 0.50-0.43 (m, 1 H), 0.31-0.15 (m, 3 H); ^{13}C NMR (C_6D_6) δ 159.69, 145.56, 134.95, 132.90, 132.78, 131.32, 130.29, 121.40, 114.04, 113.91, 113.46, 78.36, 78.28, 73.65, 62.16, 59.05, 54.79, 37.65, 36.16, 33.95, 28.36, 21.97, 17.92, 14.17, 12.17, 10.91, 10.11; MS (ESI) *m/z* (intensity) 632 ([M+H+H_2O]$^+$, 100), 614 ([M+H]$^+$, 88), 397 (84), 313 (30), 218 (35); HRMS (ESI) *m/z* calculated for $C_{37}H_{45}NO_5P$ (M+H) 614.3035, found 614.3077.



224

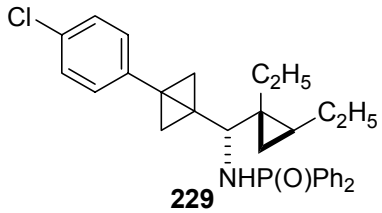
(*S)-[(1*R**,2*S**)-2-(2-{*P*,*P*-Diphenylphosphinoylamino-[1-(2-phenylallyl)cyclopropyl]-methyl}cyclopropyl)ethyl]-(4-methylphenylsulfonyl)carbamic acid ethyl ester (224).** According to the General Protocol F, Cp_2ZrHCl (0.12 g, 0.46 mmol), **223** (0.14 g, 0.46 mmol), Me_2Zn (0.23 mL, 0.46 mmol, 2.0 M in toluene), **201** (0.10 g, 0.30 mmol), CH_2I_2 (0.20 mL, 2.4 mmol) and Et_2Zn (0.15 g, 1.2 mmol) in $Cl(CH_2)_2Cl$ (3.0 mL) afforded **225** (92 mg, 43%) as a colorless foam: IR (neat) 3218, 3057, 2993, 2926, 1731, 1624, 1597, 1438, 1371, 1353, 1266, 1186, 1171, 1123 cm^{-1}; ^{1}H NMR (C_6D_6) δ 8.16-8.00 (m, 7 H), 7.39-7.35 (m, 2 H), 7.23-7.04 (m,

8 H). 6.77 (d, *J* = 8.1 Hz, 2 H), 5.26 (d, *J* = 1.4 Hz, 1 H), 5.09 (bs, 1 H), 4.16 (t, *J* = 7.4 Hz, 2 H), 3.83-3.73 (m, 2 H), 3.11-3.03 (m, 2 H), 2.45 (d, *J* = 14.8 Hz, 1 H), 2.36 (app q, *J* = 9.4 Hz, 1 H), 2.18-2.07 (m, 1 H), 1.85 (s, 3 H), 1.69-1.56 (m, 1 H), 0.76 (t, *J* = 7.1 Hz, 3 H), 0.67-0.58 (m, 1 H), 0.54-0.48 (m, 1 H), 0.39-0.18 (m, 6 H); ^{13}C NMR (C_6D_6) δ 152.61, 146.40, 143.81, 142.53, 138.33, 136.27, 135.52, 134.58, 133.83, 132.87, 132.75, 132.67, 132.55, 131.56, 131.53, 131.46, 131.43, 129.29, 128.78, 128.66, 128.53, 126.72, 115.13, 62.92, 61.39, 47.64, 38.34, 35.06, 24.64, 24.55, 23.58, 23.53, 21.12, 15.80, 13.88, 11.86, 10.70, 10.16; MS (EI) *m/z* (intensity) 696 (M^+, 1), 494 (3), 353 (3), 216 (54), 199 (63), 105 (100); HRMS (EI) *m/z* calculated for $C_{40}H_{45}N_2O_5PS$ 696.2787, found 696.2804.



227

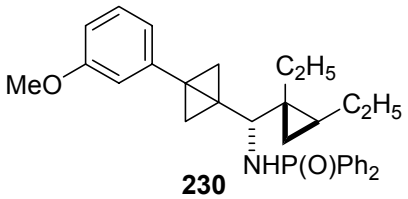
***N*-[1-(2-Phenylallyl)cyclopropylmethyl]-*P*,*P*-diphenylphosphinamide (227).** To a solution of **226** (65 mg, 0.20 mmol) at 0 °C in $Cl(CH_2)_2Cl$ (1.0 mL) was added Me_2Zn (98 μL, 0.20 mmol, 2.0 M in toluene). The reaction mixture was warmed to r.t., stirred for 1 h, cooled to –20 °C, transferred via canula to a mixture of $Zn(CH_2I)_2$ (0.59 mmol) in $Cl(CH_2)_2Cl$ (1.0 mL), warmed to r.t. and stirred for 4 h. The solution was quenched with saturated NH_4Cl, diluted with EtOAc and filtered through Celite/Florisil (1:1). The aqueous layer was extracted with EtOAc (2x) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (2:3, hexanes/EtOAc containing 1% Et_3N) to yield **227** (45 mg, 61%) as a colorless oil: IR (neat) 3203, 2955, 2924, 2854, 1437, 1186, 1162, 1123, 1108 cm^{-1}; ^{1}H NMR (C_6D_6) δ 8.04-7.96 (m, 4 H), 7.35-7.28 (m, 2 H), 7.13-7.04 (m, 9 H), 5.21 (d, *J* = 1.6 Hz, 1 H), 5.06 (d, *J* = 1.3 Hz, 1 H), 2.88-2.74 (m, 3 H), 2.58 (s, 2 H), 0.21-0.13 (m, 4 H); ^{13}C NMR (C_6D_6) δ 146.61, 142.69, 135.21, 133.52, 132.69, 132.57, 131.50, 131.46, 126.72, 114.66, 47.75, 39.16, 20.44, 20.33, 10.90; MS (EI) *m/z* (intensity) 387 (M^+, 4), 359 (5), 318 (5), 230 (43), 218 (93), 201 (100), 170 (63), 155 (27); HRMS (EI) *m/z* calculated for $C_{25}H_{26}NOP$ 387.1752, found 387.1741.



229

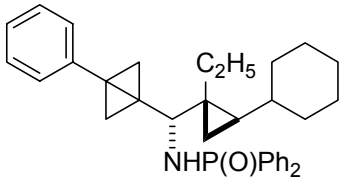
***N*-[(*S**)-[3-(4-Chlorophenyl)bicyclo[1.1.0]but-1-yl]-((1*S**,2*S**)-1,2-diethylcyclopropyl)methyl]-*P*,*P*-diphenylphosphinamide (229). General Protocol H.** To a suspension of Cp_2ZrHCl (80 mg, 0.31 mmol) in CH_2Cl_2 (2.0 mL) was added **136** (35 μL, 0.31 mmol) and the reaction mixture was stirred for 10 min. The solvent was removed *in vacuo* and the residue was dissolved in $Cl(CH_2)_2Cl$ (1.0 mL), cooled to –30 °C, treated with Me_2Zn (0.16 mL, 0.31 mmol, 2.0 M in toluene) and warmed to 0 °C. After addition of **211** (75 mg, 0.21 mmol), the reaction mixture was stirred for 2 h, cooled to –20 °C and transferred via canula to a mixture of $Zn(CH_2I)_2$ (0.52 mmol) in $Cl(CH_2)_2Cl$ (1.0 mL). The solution was warmed to 0 °C and stirred for 4 h. $Zn(CH_2I)_2$ was prepared by dropwise addition of CH_2I_2 (83 μL, 1.0 mmol) to a freshly prepared solution of Et_2Zn (64 mg, 0.52 mmol) in $Cl(CH_2)_2Cl$ (1.0 mL) at –20 °C. The reaction mixture was quenched with saturated NH_4Cl, diluted with EtOAc, filtered through Celite/Florisil (1:1) and the layers were separated. The aqueous layer was extracted with EtOAc (2x) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude reaction was dissolved in acetone (1.0 mL) and H_2O (1.0 mL) and treated with OsO_4 (11 mg, 43 μmol) and NMO (48 mg, 0.42 mmol) and the reaction was stirred for 1.5 h. The mixture was extracted with EtOAc (3x) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (3:2, hexanes/EtOAc containing 1% Et_3N) to yield **229** (52 mg, 51%) as a colorless foam: IR (neat) 3226, 3055, 2959, 2928, 2871, 1592, 1486, 1438, 1189, 1123, 1108 cm^{-1}; ^1H NMR (C_6D_6) δ 7.90-7.82 (m, 2 H), 7.65-7.56 (m, 2 H), 7.15-7.12 (m, 2 H), 7.07-6.94 (m, 8 H), 2.88 (dd, *J* = 10.4, 7.7 Hz, 1 H), 2.59 (dd, *J* = 10.4, 3.7 Hz, 1 H), 2.06, 2.04 (AB, *J* = 6.7 Hz, 2 H), 1.80-7.74 (m, 1 H), 1.72-1.60 (m, 1 H), 1.36-1.22 (m, 1 H), 1.03-0.81 (m, 1 H), 1.00 (t, *J* = 7.0 Hz, 3 H), 0.90 (s, 1 H), 0.84 (t, *J* = 7.5 Hz, 3 H), 0.81 (s, 1 H), 0.42-0.32 (m, 2 H), -0.09--0.16 (m, 1 H); ^{13}C NMR (C_6D_6) δ 136.53, 135.54, 134.36, 133.83, 132.72, 132.60, 132.56, 132.44, 131.49, 131.12, 128.74, 128.58, 56.87, 32.72, 31.54, 30.32, 30.28, 29.63, 29.51, 26.29, 22.52, 21.11, 19.38, 15.93, 14.55, 12.81; MS (EI) *m/z* (intensity) 489 (M^+, 5), 460 (5), 432

(6), 326 (31), 288 (25), 218 (52), 201 (100), 124 (24), 77 (44); HRMS (EI) *m/z* calculated for $C_{30}H_{33}NOPCl$ 489.1988, found 489.1991.



230

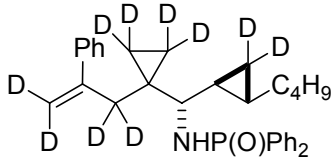
***N*-[(*S**)-[3-(3-Methoxyphenyl)bicyclo[1.1.0]but-1-yl]-((1*S**,2*S**)-1,2-diethylcyclopropyl)methyl]-*P*,*P*-diphenylphosphinamide (230).** According to the General Protocol H, Cp_2ZrHCl (80 mg, 0.31 mmol), **136** (35 μL, 0.31 mmol), Me_2Zn (0.16 mL, 0.31 mmol, 2.0 M in toluene), **207** (75 mg, 0.21 mmol), CH_2I_2 (83 μL, 1.0 mmol) and Et_2Zn (64 mg, 0.52 mmol) in $Cl(CH_2)_2Cl$ (2.0 mL) afforded **230** (54 mg, 53%) as a colorless oil: IR (neat) 3212, 3057, 2960, 2930, 2872, 1683, 1599, 1485, 1463, 1454, 1438, 1287, 1193, 1123, 1109 cm^{-1}; ^1H NMR (C_6D_6) δ 8.00-7.92 (m, 2 H), 7.66-7.57 (m, 2 H), 7.13-7.06 (m, 4 H), 7.03-6.98 (m, 4 H), 6.90-6.87 (m, 1 H), 6.65 (ddd, *J* = 8.2, 2.5, 0.8 Hz, 1 H), 3.40 (s, 3 H), 2.92 (dd, *J* = 10.3, 7.0 Hz, 1 H), 2.66 (dd, *J* = 10.3, 3.4 Hz, 1 H), 2.16 (d, *J* = 6.6 Hz, 1 H), 2.03 (d, *J* = 6.6 Hz, 1 H), 1.97-1.88 (m, 1 H), 1.82-1.70 (m, 1 H), 1.41-1.28 (m, 1 H), 1.05 (t, *J* = 7.1 Hz, 3 H), 1.00-0.91 (m, 1 H), 0.96 (s, 1 H), 0.87 (t, *J* = 7.5 Hz, 3 H), 0.82 (s, 1 H), 0.46 (dd, *J* = 8.9, 4.5 Hz, 1 H), 0.39-0.35 (m, 1 H), -0.10 (t, *J* = 5.3 Hz, 1 H); ^{13}C NMR (C_6D_6) δ 160.57, 139.58, 135.93, 134.21, 134.17, 132.94, 132.82, 132.48, 131.43, 131.39, 131.33, 129.68, 118.67, 112.18, 110.95, 57.43, 54.75, 32.66, 30.98, 30.42, 30.39, 29.36, 29.23, 26.63, 22.59, 21.08, 19.39, 15.82, 14.56, 12.83; MS (EI) *m/z* (intensity) 485 (M^+, 4), 218 (25), 201 (100), 124 (34), 91 (45); HRMS (EI) *m/z* calculated for $C_{31}H_{36}NO_2P$ 485.2484, found 485.2476.



232

***N*-[(*S**)-((1*S**,2*S**)-2-Cyclohexyl-1-ethylcyclopropyl)-(3-phenylbicyclo[1.1.0]but-1-yl)methyl]-*P*,*P*-diphenylphosphonamide (232).** To a suspension of Cp_2ZrHCl (78 mg, 0.30 mmol) in dry THF (2.0 mL) was added **231** (33 mg, 0.24 mmol). The reaction mixture was heated at 50 °C for 1.5 h, treated with an additional portion of **231** (8.0 mg, 59 μmol) and stirred

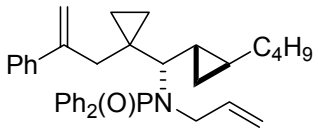
for 10 min. The mixture was cooled to r.t., all volatile material was removed *in vacuo* and the residue was dissolved in $Cl(CH_2)_2Cl$ (1.0 mL), cooled to –30 °C, treated with Me_2Zn (0.15 mL, 0.30 mmol, 2.0 M in toluene) and warmed to 0 °C. After addition of **201** (50 mg, 0.15 mmol), the reaction mixture was heated in a microwave (300W, 90 °C) for 0.5 h, cooled to –20 °C and transferred via canula to a precooled flask containing $Zn(CH_2I)_2$ (1.5 mmol) in $Cl(CH_2)_2Cl$ (1.0 mL). The mixture was stirred at -20 °C 6 h, carefully quenched with saturated NH_4Cl, diluted with EtOAc and filtered through Celite/Florisil (1:1). The aqueous layer was extracted with EtOAc (2x) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude reaction was dissolved in acetone (1.0 mL) and H_2O (1.0 mL) and treated with OsO_4 (7.6 mg, 30 μmol) and NMO (35 mg, 0.30 mmol) and the reaction was stirred for 1.5 h. The mixture was extracted with EtOAc (3x) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (3:2, hexanes/EtOAc containing 1% Et_3N) to yield **232** (42 mg, 55%) as a colorless oil: IR (neat) 3212, 3056, 2960, 2922, 2848, 1602, 1438, 1194, 1122, 1109 cm^{-1}; ^1H NMR (C_6D_6) δ 7.85-7.78 (m, 2 H), 7.70-7.63 (m, 2 H), 7.29-7.17 (m, 4 H), 7.07-6.94 (m, 7 H), 3.08 (dd, *J* = 10.9, 8.2 Hz, 1 H), 2.60 (dd, *J* = 10.9, 4.0 Hz, 1 H), 2.12-2.07 (m, 1 H), 2.12 (d, *J* = 6.6 Hz, 1 H), 2.01 (d, *J* = 6.6 Hz, 1 H), 1.81-1.64 (m, 5 H), 1.35-1.03 (m, 7 H), 0.93-0.88 (m, 2 H), 0.86-0.74 (m, 1 H), 0.80 (t, *J* = 7.4 Hz, 3 H), 0.37 (dt, *J* = 9.3, 6.0 Hz, 1 H), -0.044 (t, *J* = 5.8 Hz, 1 H); ^{13}C NMR (C_6D_6) δ 137.79, 133.11, 132.99, 132.91, 132.79, 131.37, 131.33, 131.30, 128.59, 128.51, 126.70, 125.45, 55.49, 38.79, 34.45, 33.96, 32.54, 31.25, 31.22, 30.61, 30.26, 30.14, 29.41, 27.05, 27.00, 26.91, 21.78, 20.21, 15.09, 12.32; MS (EI) *m/z* (intensity) 509 (M^+, 12), 480 (8), 426 (10), 398 (15), 392 (20) 380 (25), 308 (38), 218 (65), 201 (100); HRMS (EI) *m/z* calculated for $C_{34}H_{40}NOP$ 509.2848, found 509.2847.



233

Deuterated 202 (**233**). To a suspension of Cp_2ZrHCl (0.12 g, 0.46 mmol) in CD_2Cl_2 (1.0 mL) was added **108** (52 μL, 0.46 mmol). The reaction mixture was stirred for 5 min, cooled to -78 °C, treated with Me_2Zn (0.23 mL, 0.46 mmol, 2.0 M in toluene) and warmed to 0 °C. After addition of **201** (50 mg, 0.15 mmol), the solution was heated at reflux for 2 h, cooled to 0 °C and

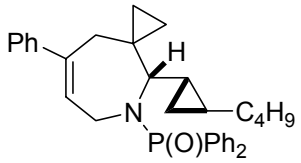
added via canula to a cooled (-20 °C) mixture of $Zn(CD_2I)_2$ (0.61 mmol) in dry CD_2Cl_2 (1.0 mL + 0.50 mL for flask washing). The reaction mixture was warmed to r.t., stirred for 3 h and quenched with sat. NH_4Cl. $Zn(CD_2I)_2$ was prepared by dropwise addition of CD_2I_2 (99 μL, 1.2 mmol) to a cooled (-20 °C) solution of Et_2Zn (75 mg, 0.61 mmol) in dry CD_2Cl_2 (1.0 mL). The reaction mixture was diluted with EtOAc, filtered through Celite/Florisil (1:1) and the layers were separated. The aqueous layer was extracted with EtOAc (2x) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (1:1, hexanes/EtOAc containing 1% v/v Et_3N) to afford **233** (38 mg, 51%) as a light yellow oil: IR (neat) 3210, 3056, 2955, 2924, 2870, 2854, 1438, 1187, 1123, 1109 cm^{-1}; ^1H NMR δ 8.10-7.99 (m, 5 H), 7.41 (d, *J* = 7.0 Hz, 3 H), 7.12-7.05 (m, 7 H), 3.14 (bt, *J* = 7.7 Hz, 1 H), 2.39 (q, *J* = 9.1 Hz, 1 H), 1.48-1.35 (m, 6 H), 0.93 (t, *J* = 6.7 Hz, 3 H), 0.74-0.70 (m, 1 H), 0.51 (dd, *J* = 9.0, 4.2 Hz, 1 H); ^{13}C NMR δ 146.07, 142.50, 135.98, 135.70, 134.29, 134.01, 132.78, 132.67, 132.56, 131.86, 131.72, 131.44, 61.60, 33.89, 32.19, 24.05, 23.98, 23.40, 23.34, 23.06, 17.92, 14.42, 9.86; MS (EI) *m/z* (intensity) 493 (M^+, 17), 328 (26), 220 (47), 201 (100); HRMS (EI) *m/z* calculated for $C_{32}H_{28}D_{10}NOP$ 493.3319, found 493.3330.



251

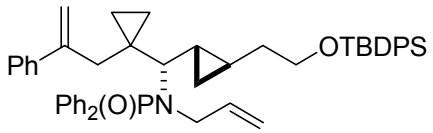
***N*-Allyl-*N*-(*S**)-(((1*S**,2*S**)-2-butylcyclopropyl)(1-(2-phenylallyl)cyclopropyl)methyl)-*P*,*P*-diphenylphosphinamide (251)**. **General Protocol I**. To a suspension of NaH (50 mg, 2.1 mmol) in dry THF (3.0 mL) was added **202** (0.20 g, 0.41 mmol). The reaction mixture was stirred for 20 min, treated with HMPA (0.36 mL, 2.1 mmol) and allyl iodide (0.38 mL, 4.1 mmol), heated at 70 °C for 1 h, cooled to r.t., quenched with sat. NH_4Cl and extracted with EtOAc (3x). The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (3:1, hexanes/EtOAc containing 1% v/v Et_3N) to afford **251** (0.21 g, 95%) as a colorless foam: IR (neat) 3057, 2955, 2924, 2854, 1438, 1203, 1118, 1104 cm^{-1}; ^1H NMR (C_6D_6) δ 8.05-7.98 (m, 4 H), 7.56-7.52 (m, 2 H), 7.21-7.15 (m, 2 H), 7.12-7.02 (m, 7 H), 6.19-6.05 (m, 1 H), 5.37 (d, *J* = 1.4 Hz, 1 H), 5.10 (d, *J* = 1.2 Hz, 1 H), 4.81-4.75 (m, 2 H), 4.01-3.78 (m, 2 H), 3.53-3.46 (m, 1 H), 3.38 (d, *J* = 15.5 Hz, 1 H), 2.54 (d, *J* = 15.6 Hz, 1 H), 1.84-1.76 (m, 1 H), 1.43-1.29 (m, 4 H),

1.09-0.88 (m, 3 H), 0.95 (t, J = 6.9 Hz, 3 H), 0.70-0.51 (m, 2 H), 0.45-0.36 (m, 2 H), 0.22-0.16 (m, 1 H), 0.14-0.08 (m, 1 H); ^{13}C NMR (C_6D_6) δ 145.86, 142.79, 139.72, 139.68, 135.59, 135.02, 133.95, 133.36, 133.17, 133.10, 133.05, 132.98, 131.31, 131.27, 128.58, 126.61, 115.11, 114.43, 63.38, 47.45, 47.39, 39.78, 33.71, 31.95, 23.01, 19.98, 19.91, 17.61, 15.14, 14.43, 10.03, 7.61; MS (EI) *m/z* (rel. intensity) 523 (M^+, 3), 366 (75), 201 (100); HRMS (EI) *m/z* calculated for $C_{35}H_{42}NOP$ 523.3004, found 523.3016.



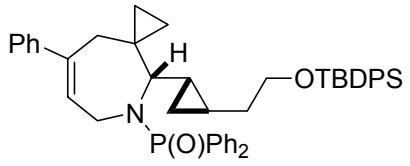
252

(4*S)-4-((1*S**,2*S**)-2-Butylcyclopropyl)-5-(diphenylphosphinoyl)-8-phenyl-5-azaspiro[2.6]-non-7-ene (252)**. **General Protocol J**. To a solution of **251** (0.15 g, 0.29 mmol) in dry CH_2Cl_2 (57 mL) was added 1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro-(phenylmethylene)tricyclohexylphosphine)ruthenium (24 mg, 0.029 mmol). The reaction mixture was heated at reflux for 7 h, cooled to r.t., filtered through Celite and concentrated. The residue was purified by chromatography on deactivated SiO_2 (3:2, hexanes/EtOAc containing 1% v/v Et_3N) to afford **252** (0.11 g, 75%) as a colorless foam: IR (neat) 3057, 2998, 2954, 2924, 2870, 2853, 1635, 1592, 1492, 1437, 1205, 1120, 1107 cm^{-1}; ^{1}H NMR (C_6D_6) δ 8.06-7.92 (m, 4 H), 7.20-7.03 (m, 11 H), 5.49 (dd, J = 6.4, 3.5 Hz, 1 H), 3.98-3.88 (m, 1 H), 3.61 (ddd, J = 17.4, 9.9, 6.9 Hz, 1 H), 3.03 (t, J = 8.9 Hz, 1 H), 2.78 (d, J = 16.5 Hz, 1 H), 2.48 (d, J = 16.5 Hz, 1 H), 1.65-1.56 (m, 1 H), 1.40-1.35 (m, 4 H), 1.03-0.85 (m, 3 H), 0.94 (t, J = 6.3 Hz, 3 H), 0.81-0.78 (m, 1 H), 0.67-0.63 (m, 1 H), 0.39-0.26 (m, 4 H); ^{13}C NMR (C_6D_6) δ 144.86, 144.22, 135.39, 135.34, 133.71, 133.06, 132.93, 132.80, 131.42, 131.38, 131.33, 131.30, 127.13, 127.08, 126.22, 65.18, 65.14, 41.85, 41.78, 40.30, 34.22, 32.02, 23.98, 23.91, 23.09, 22.99, 19.55, 17.21, 14.42, 13.56, 13.16, 12.30; MS (EI) *m/z* (rel. intensity) 495 (M^+, 12), 398 (9), 294 (45), 201 (100); HRMS (EI) *m/z* calculated for $C_{33}H_{38}NOP$ 495.2691, found 495.2686.



253

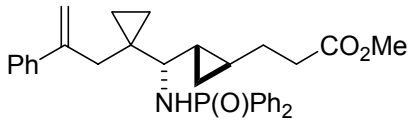
***N*-Allyl-*N*-(*S**)-{{(1*S**,2*R**)-2-[2-(*tert*-butyldiphenylsilanyloxy)ethyl]cyclopropyl}-[1-(2-phenylallyl)cyclopropyl]methyl}-*P*,*P*-diphenylphosphinamide (253)**. According to the General Protocol I, **219** (0.15 g, 0.21 mmol), NaH (25 mg, 1.1 mmol), and HMPA (0.19 mL, 1.1 mmol), allyl iodide (0.18 mL, 2.1 mmol) in dry THF (2.0 mL) afforded **253** (0.14 g, 88%) as a colorless foam: IR (neat) 3055, 3013, 2929, 2857, 1625, 1472, 1438, 1428, 1204, 1112 cm^{-1}; ^1H NMR (C_6D_6) δ 8.07-7.97 (m, 4 H), 7.87-7.84 (m, 4 H), 7.57-7.54 (m, 2 H), 7.29-7.18 (m, 8 H), 7.11-6.99 (m, 7 H), 6.15-6.02 (m, 1 H), 5.35 (d, *J* = 1.1 Hz, 1 H), 5.06 (s, 1 H), 4.79-4.74 (m, 2 H), 3.97-3.75 (m, 4 H), 3.42-3.33 (m, 2 H), 2.56 (d, *J* = 15.7 Hz, 1 H), 2.29-2.18 (m, 1 H), 1.22 (s, 9 H), 1.14-1.08 (m, 1 H), 1.02-0.87 (m, 3 H), 0.60-0.51 (m, 1 H), 0.42-0.34 (m, 2 H), 0.16-0.07 (m, 2 H); ^{13}C NMR (C_6D_6) δ 145.87, 142.75, 139.54, 136.02, 135.33, 135.00, 134.51, 134.46, 133.68, 133.34, 133.22, 133.11, 132.99, 131.29, 129.91, 128.55, 126.61, 115.26, 114.38, 64.34, 63.49, 47.43, 39.69, 37.25, 27.18, 19.99, 19.92, 19.48, 14.89, 14.58, 10.03, 7.58; MS (ESI) *m/z* (rel. intensity) 750 ($[M+H]^+$, 100), 672 (58); HRMS (ESI) *m/z* calculated for $C_{49}H_{57}NO_2PSi$ (M+H) 750.3896, found 750.3871.



254

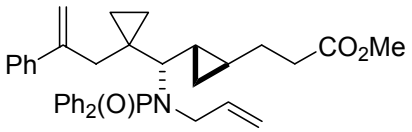
(4*S)-4-{2-[(1*S**,2*R**)-2-(*tert*-Butyldiphenylsilanyloxy)ethyl]cyclopropyl}-5-(diphenylphosphinoyl)-8-phenyl-5-azaspiro[2.6]non-7-ene (254)**. According to the General Protocol J, **253** (0.13 g, 0.17 mmol) and 1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro-(phenylmethylene)tricyclohexylphosphine)ruthenium (15 mg, 0.017 mmol) in CH_2Cl_2 (35 mL) afforded **254** (89 mg, 71%) as a colorless foam: IR (neat) 3070, 2998, 2929, 2856, 1437, 1428, 1206, 1108 cm^{-1}; ^1H NMR (C_6D_6) δ 8.02-7.93 (m, 5 H), 7.85-7.80 (m, 4 H), 7.28-7.22 (m, 8 H), 7.18-7.12 (m, 2 H), 7.10-7.07 (m, 3 H), 7.03-7.00 (m, 3 H), 5.48 (dd, *J* = 6.6, 3.7 Hz, 1 H), 3.88-3.71 (m, 3 H), 3.53 (ddd, *J* = 17.3, 10.2, 7.2 Hz, 1 H), 2.91 (app t, *J* = 8.8 Hz, 1 H), 2.74 (d, *J* = 16.4 Hz, 1 H), 2.44 (d, *J* = 16.5 Hz, 1 H), 2.02-1.91 (m, 1 H), 1.34-1.25 (m, 1 H), 1.21 (s, 9 H),

1.01-0.82 (2 H), 0.75-0.71 (m, 1 H), 0.59-0.55 (m, 1 H), 0.32-0.23 (m, 4 H); ^{13}C NMR (C_6D_6) δ 144.85, 144.17, 136.06, 135.34, 135.26, 134.56, 133.67, 133.62, 132.98, 132.85, 131.43, 131.29, 129.87, 127.25, 127.20, 127.08, 126.21, 65.17, 64.48, 41.72, 41.66, 40.20, 37.61, 27.17, 23.93, 23.85, 19.45, 19.33, 13.96, 13.21, 13.17, 12.27; MS (ESI) *m/z* (rel. intensity) 744 ([M+Na]$^+$, 100), 722 ([M+H]$^+$, 27); HRMS (ESI) *m/z* calculated for $C_{47}H_{53}NO_2PSi$ (M+H) 722.3583, found 722.3618.



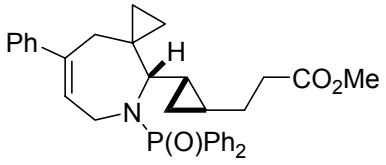
255

Methyl 3-((*1S,*2S**)-2-((*S**)-(*N*-diphenylphosphinoylamino)(1-(2-phenylallyl)cyclopropyl)-methyl)cyclopropyl)propanoate (255)**. To a solution of **220** (90 mg, 0.14 mmol) in dry THF (2.0 mL) was added TBAF (0.21 mL, 0.21 mmol, 1.0 M in THF). The reaction mixture was stirred for 1 h, diluted with water and 10% HCl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was dissolved in MeOH (2.0 mL) and treated with $TMSCHN_2$ (0.14 mL, 0.27 mmol, 2.0 M in hexanes). The mixture was stirred for 1 h, quenched with sat. NH_4Cl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (2:3, hexanes/EtOAc containing 1% v/v Et_3N) to afford **255** (61 mg, 87%) as a colorless oil: IR (neat) 3209, 3057, 2997, 2949, 2925, 2861, 1736, 1437, 1187, 1123, 1109 cm^{-1}; ^{1}H NMR (C_6D_6) δ 8.11-7.98 (m, 4 H), 7.41-7.37 (m, 2 H), 7.18-7.04 (m, 9 H), 5.26 (d, *J* = 1.5 Hz, 1 H), 5.04 (bs, 1 H), 3.41 (dd, *J* = 9.6, 6.0 Hz, 1 H), 3.30 (s, 3 H), 3.01 (d, *J* = 14.8 Hz, 1 H), 2.59 (d, *J* = 14.8 Hz, 1 H), 2.41-2.28 (m, 3 H), 1.64-1.52 (m, 1 H), 1.47-1.33 (m, 1 H), 0.93-0.83 (m, 1 H), 0.66-0.57 (m, 1 H), 0.47-0.43 (m, 1 H), 0.39-0.25 (m, 4 H), 0.14 (dt, *J* = 8.3, 5.0 Hz, 1 H); ^{13}C NMR (C_6D_6) δ 173.89, 146.05, 142.51, 136.16, 135.63, 134.48, 133.93, 132.92, 132.79, 132.64, 132.52, 131.44, 131.40, 131.35, 128.52, 128.47, 127.59, 126.66, 115.00, 61.30, 50.92, 37.97, 34.08, 29.53, 24.35, 24.27, 24.09, 24.04, 17.59, 12.26, 10.43, 10.00; MS (EI) *m/z* (rel. intensity) 513 (M$^+$, 32), 356 (29), 296 (34), 218 (100), 201 (75); HRMS (EI) *m/z* calculated for $C_{32}H_{36}NO_3P$ 513.2433, found 513.2438.



256

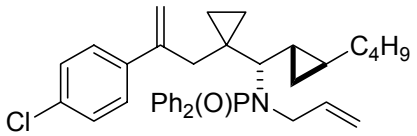
Methyl 3-((1*S,2*S**)-2-((*S**)-(*N*-allyl-(*P*,*P*-diphenylphosphinoylamino))(1-(2-phenylallyl)-cyclopropyl)methyl)cyclopropyl)propanoate (256)**. To a suspension of NaH (23 mg, 0.58 mmol) in dry THF (1.0 mL) was added a solution of **255** (60 mg, 0.12 mmol) in dry THF (0.50 mL). The reaction mixture was stirred for 20 min, treated with HMPA (0.36 mL, 2.1 mmol) and allyl iodide (0.38 mL, 4.1 mmol), heated at 70 °C for 1 h, cooled to r.t., quenched with sat. NH_4Cl and extracted with EtOAc (3x). The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4) and concentrated. The residue was dissolved in MeOH (2.0 mL) and treated with $TMSCHN_2$ (0.12 mL, 0.23 mmol, 2.0 M in hexanes) and the mixture was stirred for 1 h, quenched with sat. NH_4Cl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (3:2, hexanes/EtOAc containing 1% v/v Et_3N) to afford **256** (42 mg, 65%) as a colorless oil: IR (neat) 3057, 2994, 2923, 1736, 1438, 1199, 1118 cm^{-1}; ^1H NMR (C_6D_6) δ 8.07-7.98 (m, 4 H), 7.54-7.51 (m, 2 H), 7.21-7.03 (m, 9 H), 6.14-6.01 (m, 1 H), 5.35 (s, 1 H), 5.05 (d, *J* = 1.1 Hz, 1 H), 4.78-4.73 (m, 2 H), 3.98-3.73 (m, 2 H), 3.40 (s, 3 H), 3.40-3.31 (m, 2 H), 2.49 (d, *J* = 15.7 Hz, 1 H), 2.37-2.31 (m, 2 H), 2.12-2.02 (m, 1 H), 1.15-0.91 (m, 2 H), 0.87-0.84 (m, 2 H), 0.57-0.48 (m, 1 H), 0.38-0.35 (m, 2 H), 0.11--0.01 (m, 2 H); ^{13}C NMR (C_6D_6) δ 173.54, 139.50, 135.35, 134.72, 133.70, 133.25, 133.14, 133.06, 133.02, 131.38, 131.34, 131.31, 128.60, 126.56, 115.33, 114.35, 105.50, 63.28, 50.98, 47.33, 47.27, 39.70, 33.87, 29.37, 20.28, 19.85, 19.78, 17.08, 14.80, 10.00, 7.57; MS (ESI) *m/z* (rel. intensity) 576 ($[M+Na]^+$, 92), 554 ($[M+H]^+$, 100), 258 (57); HRMS (ESI) *m/z* calculated for $C_{35}H_{41}NO_3P$ (M+H) 554.2824, found 554.2819.



257

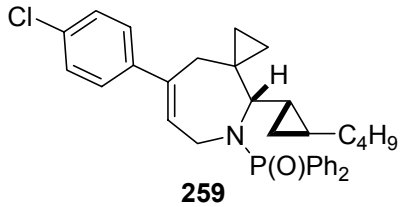
3-{(1*S,2*S**)-2-[(4*S**)-5-(Diphenylphosphinoyl)-8-phenyl-5-azaspiro[2.6]non-7-en-4-yl]cyclopropyl}propionic acid methyl ester (257)**. According to the General Protocol J, **256** (16 mg, 0.029 mmol) and 1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro-

(phenylmethylene)tricyclohexylphosphine)ruthenium (2.5 mg, 2.9 μmol) in CH_2Cl_2 (6.0 mL) afforded **9c** (9.6 mg, 63%) as a colorless oil: IR (neat) 3048, 2999, 2925, 1734, 1437, 1195, 1120, 1107 cm^{-1}; ^1H NMR (C_6D_6) δ 8.08-7.92 (m, 4 H), 7.20-7.09 (m, 7 H), 7.04-7.01 (m, 3 H), 5.49 (dd, *J* = 6.7, 3.9 Hz, 1 H), 3.92-3.79 (m, 1 H), 3.58 (ddd, *J* = 17.5, 10.3, 7.1 Hz, 1 H), 3.40 (s, 1 H), 2.83 (app t, *J* = 8.8 Hz, 1 H), 2.71 (d, *J* = 16.6 Hz, 1 H), 2.47-2.26 (m, 3 H), 1.87-1.75 (m, 1 H), 1.40-1.28 (m, 1 H), 1.02-0.95 (m, 1 H), 0.93-0.84 (m, 1 H), 0.69-0.62 (m, 1 H), 0.60-0.52 (m, 1 H), 0.30-0.18 (m, 4 H); ^{13}C NMR (C_6D_6) δ 173.61, 144.77, 144.24, 135.36, 135.01, 133.67, 133.37, 133.12, 133.00, 132.87, 131.50, 131.46, 131.33, 131.30, 128.51, 127.23, 127.18, 127.10, 126.21, 65.28, 50.93, 41.62, 41.56, 40.17, 33.98, 29.73, 23.92, 23.83, 19.67, 16.78, 13.21, 13.12, 12.16; MS (EI) *m/z* (rel. intensity) 525 (M^+, 16), 324 (38), 201 (100); HRMS (EI) *m/z* calculated for $C_{33}H_{36}NO_3P$ 525.2433, found 525.2452.



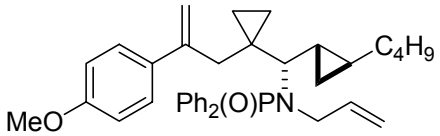
258

***N*-Allyl-*N*-(*S**)-(((*1S**,*2S**)-2-butylcyclopropyl)(1-(2-(4-chlorophenyl)allyl)cyclopropyl)-methyl)-*P*,*P*-diphenylphosphinamide (258)**. According to the General Protocol I, **217** (0.10 g, 0.19 mmol), NaH (23 mg, 0.97 mmol), HMPA (0.17 mL, 0.97 mmol), and allyl iodide (0.18 mL, 1.9 mmol) in dry THF (2.0 mL) afforded **258** (81 mg, 75%) as a colorless oil: IR (neat) 3058, 2991, 2955, 2924, 2854, 1493, 1437, 1202, 1118, 1102 cm^{-1}; ^1H NMR (C_6D_6) δ 7.99-7.92 (m, 4 H), 7.28 (d, *J* = 8.6 Hz, 2 H), 7.15-7.12 (m, 2 H), 7.05-7.03 (m, 6 H), 6.10-5.97 (m, 1 H), 5.23 (s, 1 H), 5.06 (s, 1 H), 4.80-4.75 (m, 2 H), 3.96-3.74 (m, 2 H), 3.49 (t, *J* = 9.8 Hz, 1 H), 3.29 (d, *J* = 15.7 Hz, 1 H), 2.36 (d, *J* = 15.7 Hz, 1 H), 1.77-1.72 (m, 1 H), 1.36-1.34 (m, 4 H), 1.04-0.87 (m, 6 H), 0.67-0.59 (m, 1 H), 0.56-0.47 (m, 1 H), 0.37-0.31 (m, 2 H), 0.22-0.17 (m, 1 H), 0.14-0.08 (m, 1 H); ^{13}C NMR (C_6D_6) δ 144.69, 141.20, 139.50, 133.38, 133.30, 133.03, 132.91, 131.40, 131.36, 131.32, 128.67, 115.21, 114.76, 62.94, 62.91, 47.39, 47.33, 39.69, 33.71, 31.96, 23.02, 19.97, 19.77, 19.71, 17.57, 15.18, 14.42, 10.03, 7.70; MS (EI) *m/z* (rel. intensity) 557 (M^+, 7), 366 (90), 300 (34), 258 (45), 201 (100); HRMS (EI) *m/z* calculated for $C_{35}H_{41}NOPCl$ 557.2614, found 557.2622.



259

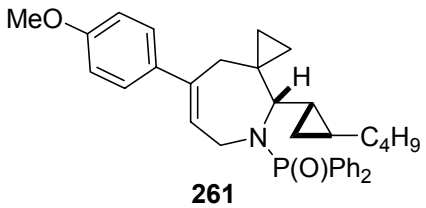
(4*S)-4-((1*S**,2*S**)-2-Butylcyclopropyl)-8-(4-chlorophenyl)-5-(diphenylphosphinoyl)-5-azaspiro[2.6]non-7-ene (259)**. According to the General Protocol J, **258** (80 mg, 0.14 mmol) and 1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)tricyclohexylphosphine)ruthenium (12 mg, 0.014 mmol) in CH_2Cl_2 (29 mL) afforded **259** (55 mg, 72%) as a colorless foam: IR (neat) 3058, 2955, 2924, 2854, 1490, 1437, 1204, 1120, 1107 cm^{-1}; ^1H NMR (C_6D_6) δ 8.00-7.88 (m, 4 H), 7.15-7.02 (m, 8 H), 6.83-6.78 (m, 2 H), 5.31 (dd, *J* = 6.5, 3.6 Hz, 1 H), 3.89 (b app t, *J* = 14.7 Hz, 1 H), 3.62-3.50 (m, 1 H), 3.05 (t, *J* = 8.4 Hz, 1 H), 2.58 (d, *J* = 16.6 Hz, 1 H), 2.37 (d, *J* = 16.7 Hz, 1 H), 1.64-1.54 (m, 1 H), 1.40-1.30 (m, 5 H), 0.96-0.91 (m, 4 H), 0.88-0.78 (m, 2 H), 0.67-0.63 (m, 1 H), 0.38-0.33 (m, 1 H), 0.31-0.22 (m, 3 H); ^{13}C NMR (C_6D_6) δ 143.12, 142.86, 135.32, 135.27, 133.69, 133.59, 133.03, 132.90, 132.87, 132.74, 131.47, 131.44, 131.35, 128.54, 127.50, 64.93, 41.82, 41.76, 40.26, 34.24, 32.01, 23.88, 23.81, 23.09, 19.49, 17.15, 14.40, 13.54, 12.89, 12.27; MS (EI) *m/z* (rel. intensity) 529 (M^+, 11), 328 (33), 201 (100); HRMS (EI) *m/z* calculated for $C_{33}H_{37}NOPCl$ 529.2301, found 529.2298.



260

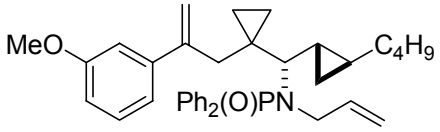
***N*-Allyl-N-(*S**)-(((*1S**,*2S**)-2-butylcyclopropyl)(1-(2-(4-methoxyphenyl)allyl)cyclopropyl)-methyl)-*P*,*P*-diphenylphosphinamide (260)**. According to the General Protocol I, **214** (0.10 g, 0.19 mmol), NaH (23 mg, 0.19 mmol), HMPA (0.17 mL, 0.97 mmol), and allyl iodide (0.18 mL, 2.0 mmol) in dry THF (3.0 mL) afforded **260** (75 mg, 69%) as a colorless foam: IR (neat) 3058, 2955, 2924, 2854, 1606, 1512, 1437, 1248, 1201, 1118 cm^{-1}; ^1H NMR (C_6D_6) δ 8.07-8.00 (m, 4 H), 7.55-7.50 (m, 2 H), 7.09-7.03 (m, 6 H), 6.84-6.79 (m, 2 H), 6.20-6.08 (m, 1 H), 5.36 (d, *J* = 1.4 Hz, 1 H), 5.04 (d, *J* = 1.0 Hz, 1 H), 4.83-4.77 (m, 2 H), 4.04-3.80 (m, 2 H), 3.48 (app. t, *J* = 9.6 Hz, 1 H), 3.40 (d, *J* = 15.4 Hz, 1 H), 3.32 (s, 3 H), 2.60 (d, *J* = 15.4 Hz, 1 H), 1.85-1.77 (m, 1 H), 1.43-1.29 (m, 4 H), 1.08-0.89 (m, 6 H), 0.71-0.52 (m, 2 H), 0.49-0.42 (m, 2 H), 0.23-0.18 (m, 1 H), 0.15-0.09 (m, 1 H); ^{13}C NMR (C_6D_6) δ 159.70, 145.16, 139.74, 139.70, 135.53, 135.06,

135.00, 133.89, 133.34, 133.23, 133.14, 133.02, 131.32, 131.28, 115.14, 114.06, 112.77, 63.73, 54.77, 47.46, 47.40, 39.79, 33.71, 31.96, 23.02, 20.05, 19.98, 19.92, 17.64, 15.17, 14.42, 9.97, 7.61; MS (EI) *m/z* (rel. intensity) 553 (M^+, 1), 366 (26), 201 (100); HRMS (EI) *m/z* calculated for $C_{36}H_{44}NO_2P$ 553.3110, found 553.3094.



261

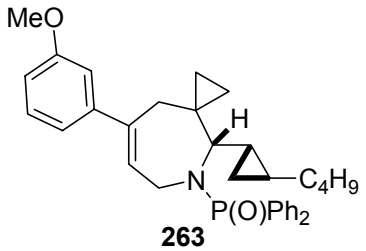
(4*S)-4-((1*S**,2*S**)-2-Butylcyclopropyl)-8-(4-methoxyphenyl)-5-(diphenylphosphinoyl)-5-azaspiro[2.6]non-7-ene (261)**. According to the General Protocol J, **260** (70 mg, 0.13 mmol) and 1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)tricyclohexylphosphine)ruthenium (11 mg, 0.013 mmol) in CH_2Cl_2 (25 mL) afforded **261** (53 mg, 80%) as a colorless foam: IR (neat) 3057, 2998, 2954, 2926, 2853, 1606, 1510, 1437, 1284, 1247, 1204, 1181, 1120 cm^{-1}; ^1H NMR (C_6D_6) δ 8.07-7.92 (m, 4 H), 7.15-7.03 (m, 8 H), 6.82-6.77 (m, 2 H), 5.51-5.47 (m, 1 H), 4.03-3.91 (m, 1 H), 3.63 (ddd, *J* = 17.1, 9.9, 7.1 Hz, 1 H), 3.35 (s, 3 H), 3.01 (t, *J* = 8.8 Hz, 1 H), 2.84 (d, *J* = 16.4 Hz, 1 H), 2.46 (d, *J* = 16.4 Hz, 1 H), 1.62-1.53 (m, 1 H), 1.44-1.30 (m, 4 H), 1.04-0.88 (m, 3 H), 0.94 (t, *J* = 6.5 Hz, 3 H), 0.82-0.79 (m, 1 H), 0.67-0.63 (m, 1 H), 0.40-0.27 (m, 4 H); ^{13}C NMR (C_6D_6) δ 159.34, 143.77, 135.55, 135.51, 133.88, 133.10, 132.98, 132.85, 131.33, 131.27, 128.42, 128.10, 127.31, 125.64, 125.59, 113.97, 65.31, 65.28, 54.84, 41.81, 41.75, 40.26, 34.27, 32.05, 23.93, 23.86, 23.11, 19.68, 17.25, 14.43, 13.61, 13.37, 12.28; MS (EI) *m/z* (rel. intensity) 525 (M^+, 17), 324 (51), 201 (100); HRMS (EI) *m/z* calculated for $C_{34}H_{40}NO_2P$ 525.2797, found 525.2794.



262

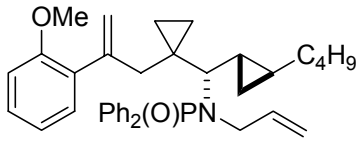
***N*-Allyl-N-(*S**)-(((*1S**,*2S**)-2-butylcyclopropyl)(1-(2-(3-methoxyphenyl)allyl)cyclopropyl)-methyl)-*P*,*P*-diphenylphosphinamide (262)**. According to the General Protocol I, **214** (0.14 g, 0.26 mmol), NaH (52 mg, 1.3 mmol), HMPA (0.23 mL, 1.3 mmol), and allyl iodide (0.24 mL, 2.6 mmol) in dry THF (3.0 mL) afforded **262** (0.14 g, 96%) as a colorless foam: IR (neat) 3058, 2954, 2923, 2854, 1597, 1576, 1437, 1202, 1118 cm^{-1}; ^1H NMR (C_6D_6) δ 8.07-7.99 (m, 5 H),

7.37-7.36 (m, 1 H), 7.22-7.12 (m, 1 H), 7.08-7.06 (m, 6 H), 6.80-6.77 (m, 1 H), 6.19-6.06 (m, 1 H), 5.43 (d, J = 1.2 Hz, 1 H), 5.11 (d, J = 0.9 Hz, 1 H), 4.83-4.77 (m, 2 H), 4.03-3.80 (m, 2 H), 3.51-3.45 (m, 1 H), 3.48 (s, 3 H), 3.40 (d, J = 15.6 Hz, 1 H), 2.61 (d, J = 15.5 Hz, 1 H), 1.83-1.75 (m, 1 H), 1.38-1.31 (m, 4 H), 1.06-0.89 (m, 3 H), 0.96 (t, J = 6.9 Hz, 3 H), 0.71-0.52 (m, 2 H), 0.49-0.39 (m, 2 H), 0.22-0.10 (m, 2 H); ^{13}C NMR (C_6D_6) δ 160.39, 146.05, 144.48, 139.68, 139.64, 135.58, 135.07, 133.94, 133.40, 133.20, 133.14, 133.08, 133.02, 131.36, 131.32, 131.26, 131.23, 129.53, 119.13, 115.12, 114.61, 113.41, 112.56, 63.66, 63.63, 54.96, 47.50, 47.44, 39.72, 33.73, 31.92, 23.00, 20.11, 20.05, 17.65, 15.15, 14.37, 10.04, 7.62; MS (EI) *m/z* (rel. intensity) 553 (M^+, 2), 366 (67), 296, 35, 201 (100); HRMS (EI) *m/z* calculated for $C_{36}H_{44}NO_2P$ 553.3110, found 553.3121.



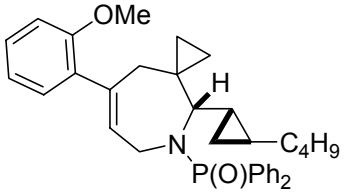
263

(4*S)-4-((1*S**,2*S**)-2-Butylcyclopropyl)-8-(3-methoxyphenyl)-5-(diphenylphosphinoyl)-5-azaspiro[2.6]non-7-ene (263)**. According to the General Protocol J, **262** (80 mg, 0.14 mmol) and 1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)tricyclohexylphosphine)ruthenium (12 mg, 0.014 mmol) in CH_2Cl_2 (29 mL) afforded **263** (57 mg, 75%) as a colorless foam: IR (neat) 3059, 2998, 2955, 2924, 2853, 1597, 1437, 1203, 1121, 1107 cm^{-1}; ^{1}H NMR (C_6D_6) δ 8.04-7.94 (m, 4 H), 7.15-7.03 (m, 7 H), 6.87-6.85 (m, 1 H), 6.81-6.79 (m, 1 H), 6.71-6.68 (m, 1 H), 5.53 (dd, J = 6.3, 3.8 Hz, 1 H), 3.99-3.87 (m, 1 H), 3.59 (ddd, J = 17.1, 10.0, 7.1 Hz, 1 H), 3.38 (s, 3 H), 3.00 (t, J = 8.7 Hz, 1 H), 2.81 (d, J = 16.4 Hz, 1 H), 2.48 (d, J = 16.5 Hz, 1 H), 1.61-1.52 (m, 1 H), 1.43-1.30 (m, 4 H), 1.01-0.81 (m, 3 H), 0.93 (t, J = 6.6 Hz, 3 H), 0.80-0.73 (m, 1 H), 0.65-0.62 (m, 1 H), 0.38-0.25 (m, 4 H); ^{13}C NMR (C_6D_6) δ 160.32, 146.57, 144.39, 135.62, 135.55, 133.92, 133.12, 133.00, 132.88, 131.35, 131.30, 129.48, 128.45, 128.14, 127.23, 127.19, 118.78, 112.71, 112.35, 65.34, 54.89, 41.94, 41.87, 40.46, 34.27, 34.10, 32.03, 24.06, 23.98, 23.10, 22.98, 19.74, 17.30, 14.37, 13.65, 13.34, 12.37; MS (EI) *m/z* (rel. intensity) 525 (M^+, 10), 324 (40), 201 (100); HRMS (EI) *m/z* calculated for $C_{34}H_{40}NO_2P$ 525.2797, found 525.2823.



264

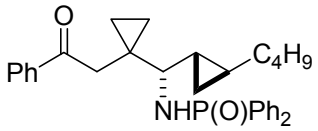
***N*-Allyl-N-(*S**)-(((*1S**,*2S**)-2-butylcyclopropyl)(1-(2-(2-methoxyphenyl)allyl)cyclopropyl)-methyl)-*P*,*P*-diphenylphosphinamide (264)**. According to the General Protocol I, **216** (57 mg, 0.11 mmol), NaH (22 mg, 0.56 mmol), HMPA (97 μL, 0.56 mmol), and allyl iodide (0.10 mL, 1.1 mmol) in dry THF (2.0 mL) afforded **264** (54 mg, 89%) as a colorless foam: IR (neat) 3046, 2950, 2923, 1489, 1436, 1204, 1117 cm^{-1}; ^1H NMR (C_6D_6) δ 8.07-7.99 (m, 4 H), 7.42 (dd, *J* = 7.4, 1.7 Hz, 1 H), 7.11-7.05 (m, 7 H), 6.86 (td, *J* = 7.4, 0.7 Hz, 1 H), 6.55 (d, *J* = 8.1 Hz, 1 H), 6.02-5.89 (m, 1 H), 5.24 (s, 1 H), 5.22 (s, 1 H), 4.81-4.72 (m, 2 H), 4.04-3.79 (m, 2 H), 3.61 (dd, *J* = 10.1, 9.1 Hz, 1 H), 3.39 (d, *J* = 15.6 Hz, 1 H), 3.34 (s, 3 H), 2.66 (d, *J* = 15.3 Hz, 1 H), 1.79-1.73 (m, 1 H), 1.36-1.31 (m, 4 H), 1.19-1.05 (m, 1 H), 0.95-0.91 (m, 5 H), 0.58-0.40 (m, 4 H), 0.24-0.18 (m, 1 H), 0.10-0.04 (m, 1 H); ^{13}C NMR (C_6D_6) δ 157.09, 146.30, 139.84, 136.56, 135.55, 134.93, 133.90, 133.69, 133.23, 133.10, 133.06, 132.93, 131.25, 131.10, 130.77, 120.97, 117.42, 114.84, 111.05, 63.03, 55.04, 47.62, 41.74, 33.70, 31.94, 23.03, 20.79, 20.72, 20.23, 17.82, 15.14, 14.39, 10.63, 8.12; MS (EI) *m/z* (rel. intensity) 553 (M^+, 1), 366 (55), 296 (30), 257 (31), 201 (100); HRMS (EI) *m/z* calculated for $C_{36}H_{44}NO_2P$ 553.3110, found 553.3101.



265

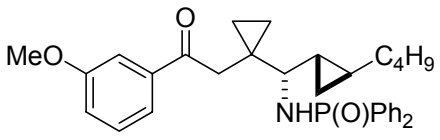
(4*S)-4-((1*S**,2*S**)-2-Butylcyclopropyl)-8-(2-methoxyphenyl)-5-(diphenylphosphinoyl)-5-azaspiro[2.6]non-7-ene (265)**. According to the General Protocol J, **264** (50 g, 0.090 mmol) and 1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)tricyclohexylphosphine)ruthenium (8.0 mg, 9.0 μmol) in CH_2Cl_2 (18 mL) afforded **265** (40 mg, 84%) as a colorless foam: IR (neat) 3058, 2997, 2954, 2925, 2853, 1488, 1437, 1249, 1204, 1119 cm^{-1}; ^1H NMR (C_6D_6) δ 8.08-8.05 (m, 4 H), 7.15-7.06 (m, 8 H), 6.92-6.88 (m, 1 H), 6.50 (d, *J* = 8.3 Hz, 1 H), 5.42 (dd, *J* = 5.7, 3.5 Hz, 1 H), 4.05-3.96 (m, 1 H), 3.65-3.53 (m, 1 H), 3.29 (s, 3 H), 3.15-2.99 (m, 1 H), 3.09 (d, *J* = 16.7 Hz, 1 H), 2.45 (d, *J* = 16.6 Hz, 1 H), 1.57-1.46 (m, 1 H), 1.50-1.25 (m, 6 H), 1.06-0.83 (m, 4 H), 0.93 (t, *J* = 6.7 Hz, 1 H), 0.68-0.63 (m, 1 H), 0.50-0.42

(m, 2 H), 0.41-0.35 (m, 1 H), 0.33-0.29 (m, 1 H); ^{13}C NMR (C_6D_6) δ 156.71, 144.62, 135.78, 135.67, 135.49, 134.14, 134.00, 133.10, 132.97, 131.28, 131.24, 131.19, 129.57, 120.84, 110.79, 65.59, 65.56, 54.72, 41.77, 41.70, 40.87, 34.25, 32.07, 24.32, 24.25, 23.11, 19.56, 17.23, 14.42, 13.60, 13.05, 11.83; MS (EI) *m/z* (rel. intensity) 525 (M^+, 12), 523 (22), 324 (36), 201 (100); HRMS (EI) *m/z* calculated for $C_{34}H_{40}NO_2P$ 525.2797, found 525.2808.



266

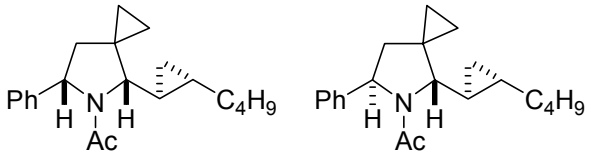
***N*-(*S**)-{((1*S**,2*S**)-2-Butylcyclopropyl)-[1-(2-oxo-2-phenylethyl)cyclopropyl]methyl}-*P*,*P*-diphenylphosphinamide (266)**. To a solution of **202** (0.15 g, 0.31 mmol) in THF (2.0 mL) and water (1.0 mL) was added $NaIO_4$ (0.33 g, 1.6 mmol) and OsO_4 (8.0 mg, 0.031 mmol). The reaction mixture was stirred for 3 h, diluted with water and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (3:2 then 2:3, hexanes/EtOAc containing 1% v/v Et_3N) to afford **266** (0.12 g, 77%) as a colorless foam: IR (neat) 3220, 3064, 2999, 2953, 2923, 2848, 1677, 1435, 1184, 1124 cm^{-1}; ^{1}H NMR (C_6D_6) δ 8.18-8.08 (m, 4 H), 7.88-7.86 (m, 2 H), 7.12-7.03 (m, 9 H), 4.64 (t, *J* = 8.7 Hz, 1 H), 3.86 (d, *J* = 17.6 Hz, 1 H), 2.49 (app q, *J* = 9.0 Hz, 1 H), 2.31 (d, *J* = 17.6 Hz, 1 H), 1.39-1.27 (m, 5 H), 1.18-1.09 (m, 1 H), 0.90-0.86 (m, 3 H), 0.78-0.71 (m, 1 H), 0.61-0.47 (m, 3 H), 0.42-0.35 (m, 2 H), 0.26-0.19 (m, 1 H), 0.16-0.12 (m, 1 H); ^{13}C NMR (C_6D_6) δ 200.57, 137.82, 136.50, 136.32, 134.84, 134.62, 132.96, 132.81, 132.69, 132.38, 132.25, 131.31, 131.27, 131.19, 131.15, 128.62, 128.56, 128.21, 61.42, 44.37, 33.89, 32.05, 23.64, 23.57, 23.01, 22.69, 22.63, 18.19, 14.39, 13.24, 11.52, 11.05; MS (EI) *m/z* (rel. intensity) 485 (M^+, 10), 326 (42), 268 (34), 218 (64), 201 (100); HRMS (EI) *m/z* calculated for $C_{31}H_{36}NO_2P$ 485.2484, found 485.2498.



267

***N*-(*S**)-{((1*S**,2*S**)-2-Butylcyclopropyl)-{1-[2-(3-methoxyphenyl)-2-oxoethyl]cyclopropyl}-methyl}-*P*,*P*-diphenylphosphinamide (267)**. To a solution of **215** (0.18 g, 0.35 mmol) in THF (3.0 mL) and water (1.5 mL) was added $NaIO_4$ (0.38 g, 1.8 mmol) and OsO_4 (10 mg, 0.035

mmol). The reaction mixture was stirred for 3 h, diluted with water and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (1:1, hexanes/EtOAc containing 1% v/v Et_3N) to afford **267** (0.10 g, 56%) as a colorless oil: IR (neat) 3228, 3059, 2998, 2955, 2924, 2854, 1676, 1596, 1582, 1464, 1437, 1258, 1191, 1123 cm^{-1}; ^1H NMR (C_6D_6) δ 8.18-8.08 (m, 4 H), 7.66 (bs, 1 H), 7.50-7.47 (m, 1 H), 7.10-7.00 (m, 7 H), 6.90-6.86 (m, 1 H), 4.55 (t, *J* = 8.4 Hz, 1 H), 3.89 (d, *J* = 17.4 Hz, 1 H), 3.27 (s, 3 H), 2.49 (app q, *J* = 9.4 Hz, 1 H), 2.36 (d, *J* = 17.5 Hz, 1 H), 1.46-1.28 (m, 6 H), 1.16-1.10 (m, 1 H), 0.88 (t, *J* = 6.8 Hz, 3 H), 0.78-0.76 (m, 1 H), 0.61-0.50 (m, 2 H), 0.45-0.35 (m, 2 H), 0.26-0.13 (m, 2 H); ^{13}C NMR (C_6D_6) δ 200.10, 159.98, 139.00, 136.15, 135.99, 134.49, 134.29, 132.42, 132.30, 132.03, 131.91, 130.91, 130.81, 129.35, 120.90, 119.36, 112.50, 61.15, 54.57, 44.03, 33.53, 31.68, 23.31, 22.63, 22.48, 17.83, 13.99, 12.74, 11.20, 10.79; MS (EI) *m/z* (rel. intensity) 515 (M^+, 0.4), 449 (10), 223 (55), 199 (48), 135 (56); HRMS (EI) *m/z* calculated for $C_{32}H_{38}NO_3P$ 515.2589, found 515.2589.



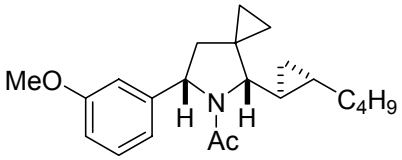
268a **268b**

1-[(4*S,6*S**)-4-((1*S**,2*S**)-2-Butylcyclopropyl)-6-phenyl-5-azaspiro[2.4]hept-5-yl]ethanone (268a) and 1-[(4*S**,6*R**)-4-((1*S**,2*S**)-2-butylcyclopropyl)-6-phenyl-5-azaspiro[2.4]hept-5-yl]ethanone (268b)**. A solution of **266** (0.14 g, 0.29 mmol) in MeOH (2.0 mL) was treated at 0 °C with a solution of HCl (2.0 mL, 2.0 M in MeOH). The reaction mixture was stirred for 1 h and concentrated. The residue was dissolved in MeOH (2.0 mL), treated with $NaBH_3CN$ (91 mg, 1.44 mmol), stirred for 4 h and concentrated. The residue was suspended in dry CH_2Cl_2 (4.0 mL), cooled to 0 °C, and treated with DIPEA (0.50 mL, 2.9 mmol) and AcCl (0.20 mL, 2.9 mmol). The reaction mixture was stirred for 4 h, quenched with sat. NH_4Cl and extracted with EtOAc (3x). The combined organic layers were washed with water, 10% HCl and brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (9:1 then 4:1 then 3:2, hexanes/EtOAc containing 1% v/v Et_3N) to afford the desired pyrrolidines **268a** (43 mg, 48%) and **268b** (20 mg, 22%) as a mixture of colorless oils.

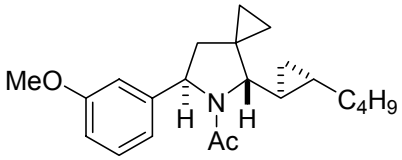
268a (major isomer): IR (neat) 3062, 2994, 2956, 2925, 2871, 1650, 1398, 1346 cm^{-1}; ^1H NMR (5.7:1 mixture of amide bond rotamers) major rotamer δ 7.38-7.27 (m, 5 H), 4.94 (t, *J* = 8.4 Hz,

1 H), 3.29 (d, *J* = 9.6 Hz, 1 H), 2.41 (dd, *J* = 11.8, 8.4 Hz, 1 H), 1.92 (dd, *J* = 12.8, 7.6 Hz, 1 H), 1.78 (s, 3 H), 1.42-1.15 (m, 7 H), 0.93-0.79 (m, 5 H), 0.90 (t, *J* = 7.1 Hz, 3 H), 0.56-0.39 (m, 4 H), 0.34-0.28 (m, 1 H); minor rotamer (representative signals) δ 5.24 (bt, 1 H), 2.86 (bd, 1 H); ^{13}C NMR δ 171.05, 144.08, 128.85, 127.12, 125.53, 68.50, 63.18, 44.99, 33.83, 31.68, 25.71, 23.07, 22.87, 22.61, 16.06, 14.16, 13.99, 10.99, 5.27; MS (EI) *m/z* (rel. intensity) 311 (M^+, 100), 255 (49), 214 (70), 172 (57); HRMS (EI) *m/z* calculated for $C_{21}H_{29}NO$ 311.2249, found 311.2244.

268b (minor isomer): IR (neat) 3061, 2994, 2957, 2923, 2855, 1650, 1397 cm^{-1}; ^{1}H NMR (6.9:1 mixture of amide bond rotamers) major rotamer δ 7.34-7.21 (m, 5 H), 5.02 (d, *J* = 8.6 Hz, 1 H), 3.54 (d, *J* = 8.2 Hz, 1 H), 3.06 (dd, *J* = 12.5, 8.8 Hz, 1 H), 1.74 (s, 3 H), 1.35-1.22 (m, 5 H), 1.24-1.18 (m, 1 H), 1.13-1.09 (m, 1 H), 0.90 (t, *J* = 6.9 Hz, 3 H), 0.86-0.79 (m, 1 H), 0.73-0.68 (m, 1 H), 0.66-0.59 (m, 1 H), 0.44-0.35 (m, 2 H), 0.26-0.17 (m, 2 H); minor rotamer (representative signals) δ 5.18 (d, *J* = 9.2 Hz, 1 H)), 3.27 (d, *J* = 6.0 Hz, 1 H), 2.90 (dd, *J* = 12.8, 9.4 Hz, 1 H), 2.16 (s, 3 H); ^{13}C NMR major rotamer δ 170.78, 144.57, 128.51, 126.93, 125.59, 67.48, 62.90, 42.57, 34.01, 31.67, 23.99, 23.53, 23.45, 22.60, 16.75, 16.17, 14.17, 9.78, 3.39; MS (EI) *m/z* (rel. intensity) 311 (M^+, 30), 214 (70), 172 (100); HRMS (EI) *m/z* calculated for $C_{21}H_{29}NO$ 311.2249, found 311.2250.



269a



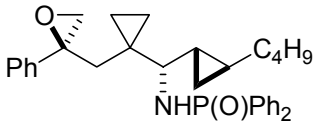
269b

1-[(4*S,6*S**)-4-((1*S**,2*S**)-2-Butylcyclopropyl)-6-(3-methoxyphenyl)-5-azaspiro[2.4]hept-5-yl]ethanone (269a) and 1-[(4*S**,6*R**)-4-((1*S**,2*S**)-2-butylcyclopropyl)-6-(3-methoxyphenyl)-5-azaspiro[2.4]hept-5-yl]ethanone (269b)**. A solution of **267** (60 mg, 0.12 mmol) in MeOH (1.5 mL) was treated at 0 °C with a solution of HCl (1.5 mL, 2.0 M in MeOH). The reaction mixture was stirred for 1 h and concentrated. The residue was dissolved in MeOH (1.0 mL), treated with $NaBH_3CN$ (37 mg, 0.58 mmol), stirred for 4 h and concentrated. The residue was suspended in dry CH_2Cl_2 (2.0 mL), cooled to 0 °C, and treated with DIPEA (0.20 mL, 1.2 mmol) and AcCl (82 μL, 1.2 mmol). The reaction mixture was stirred for 4 h, quenched with sat. NH_4Cl and extracted with EtOAc (3x). The combined organic layers were washed with water, 10% HCl and brine, dried (Na_2SO_4) and concentrated. The residue was purified by

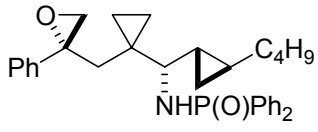
chromatography on deactivated SiO_2 (9:1 then 4:1 then 3:2, hexanes/EtOAc containing 1% v/v Et_3N) to afford a mixture of **269a** and **269b** (27 mg, 68%) as a colorless oil. The diastereomers were separated by chromatography on SiO_2 (4:1, hexanes/EtOAc) to afford **269a** (16 mg) and **269b** (9.0 mg).

269a (major isomer): IR (neat) 2995, 2956, 2925, 1648, 1601, 1397, 1262 cm^{-1}; ^1H NMR (5.9:1 mixture of amide bond rotamers) major rotamer δ 7.28 (t, *J* = 7.8 Hz, 1 H), 6.97 (d, *J* = 7.6 Hz, 1 H), 6.93 (s, 1 H), 6.81 (dd, *J* = 8.2, 2.2 Hz, 1 H), 4.91 (t, *J* = 8.3 Hz, 1 H), 3.81 (s, 3 H), 3.27 (d, *J* = 9.6 Hz, 1 H), 2.41 (dd, *J* = 12.8, 9.3 Hz, 1 H), 1.90 (dd, *J* = 12.8, 7.5 Hz, 1 H), 1.81 (s, 3 H), 1.52-1.22 (m, 6 H), 1.12-1.10 (m, 1 H), 0.92-0.79 (m, 2 H), 0.90 (t, *J* = 7.1 Hz, 3 H), 0.56-0.39 (m, 4 H), 0.34-0.30 (m, 1 H); minor rotamer (representative signals) δ 5.20 (bt, 1 H), 2.86 (bd, 1 H); ^{13}C NMR δ 171.15, 160.15, 145.85, 121.95, 117.84, 112.22, 111.42, 68.52, 63.20, 55.18, 44.96, 33.88, 31.62, 25.67, 23.07, 22.84, 22.64, 16.19, 14.07, 13.96, 10.86, 5.33; MS (EI) *m/z* (rel. intensity) 341 (M^+, 70), 244 (48), 202 (100); HRMS (EI) *m/z* calculated for $C_{22}H_{31}NO_2$ 341.2355, found 341.2355.

269b (minor isomer): IR (neat) 2995, 2956, 2923, 2854, 1651, 1601, 1397, 1261 cm^{-1}; ^1H NMR (8.1:1 mixture of amide bond rotamers) major rotamer δ 7.25-7.19 (m, 1 H), 6.85-6.76 (m, 3 H), 4.98 (d, *J* = 8.8 Hz, 1 H), 3.79 (s, 3 H), 3.53 (d, *J* = 8.3 Hz, 1 H), 3.06 (dd, *J* = 12.5, 9.1 Hz, 1 H), 1.76 (s, 3 H), 1.33-1.23 (m, 6 H), 1.27-1.19 (m, 1 H), 1.13-1.07 (m, 1 H), 0.89 (t, *J* = 6.8 Hz, 3 H), 0.85-0.80 (m, 1 H), 0.74-0.61 (m, 2 H), 0.45-0.35 (m, 1 H), 0.30-0.20 (m, 2 H); minor rotamer (representative signals) δ 5.15 (d, *J* = 9.5 Hz, 1 H)), 3.26 (d, *J* = 5.7 Hz, 1 H), 2.89 (dd, *J* = 13.3, 9.6 Hz, 1 H), 2.16 (s, 3 H); ^{13}C NMR δ 170.80, 1159.82, 146.38, 129.60, 118.07, 112.28, 111.38, 67.54, 62.87, 55.20, 42.56, 34.03, 31.69, 24.14, 23.49, 22.62, 16.78, 16.32, 14.18, 9.82, 3.54; MS (EI) *m/z* (rel. intensity) 341 (M^+, 38), 244 (58), 202 (100); HRMS (EI) *m/z* calculated for $C_{22}H_{31}NO_2$ 341.2355, found 341.2356.



270a



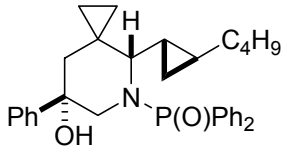
270b

***N*-(*S**)-{[(1*S**,2*S**)-2-Butylcyclopropyl](1-{[(*S**)-2-phenyloxiran-2-yl]methyl}cyclopropyl)-methyl}-*P*,*P*-diphenylphosphinamide (270a) and *N*-(*S**)-{[(1*S**,2*S**)-2-butylcyclopropyl](1-{[(*R**)-2-phenyloxiran-2-yl]methyl}cyclopropyl)methyl}-*P*,*P*-diphenylphosphinamide**

(270b). To a solution of **202** (0.15 g, 0.30 mmol) in dry CH_2Cl_2 (3.0 mL) was added *m*-CPBA (0.34 g, 1.2 mmol, ~60 wt%) in two portions (over 2 h). The reaction mixture was stirred for 4 h at r.t., filtered through basic alumina and concentrated. The residue was purified by chromatography on deactivated SiO_2 (1:1 hexanes/EtOAc containing 1% v/v Et_3N) to afford a 1:1 mixture of **270a** and **270b** (0.12 g, 77%) as a colorless oil. The diastereomers were separated by chromatography on deactivated SiO_2 (2:3 then 1:1, hexanes/EtOAc containing 1% v/v Et_3N) to afford diastereomerically pure epoxides **270a** and **270b**.

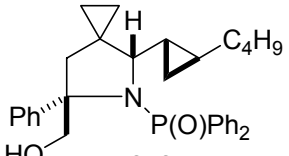
270a: IR (neat) 3225, 3058, 2995, 2955, 2923, 2854, 1437, 1188, 1123 cm^{-1}; ^1H NMR (C_6D_6) δ 8.18-8.11 (m, 2 H), 8.04-7.97 (m, 2 H), 7.26-7.23 (m, 2 H), 7.13-7.04 (m, 9 H), 4.25 (t, *J* = 10.5 Hz, 1 H), 2.60 (d, *J* = 5.7 Hz, 1 H), 2.33 (d, *J* = 15.6 Hz, 1 H), 2.28-2.21 (m, 1 H), 2.22 (d, *J* = 5.7 Hz, 1 H), 1.81 (d, *J* = 15.4 Hz, 1 H), 1.49-1.29 (m, 5 H), 1.01-0.89 (m, 1 H), 0.93 (t, *J* = 6.9 Hz, 3 H), 0.87-0.73 (m, 2 H), 0.61-0.51 (m, 2 H), 0.29 (dt, *J* = 9.2, 5.5 Hz, 1 H), 0.24-0.17 (m, 2 H), 0.10-0.07 (m, 1 H); ^{13}C NMR (C_6D_6) δ 140.96, 136.82, 136.38, 135.14, 134.70, 132.86, 132.74, 132.56, 132.43, 131.21, 128.23, 127.40, 126.35, 61.76, 60.17, 57.69, 39.68, 34.32, 32.22, 23.91, 23.85, 23.77, 23.11, 18.11, 14.43, 13.76, 11.45, 11.33; MS (EI) *m/z* (rel. intensity) 499 (M^+, 8), 481 (27), 326 (46), 218 (43), 201 (100); HRMS (EI) *m/z* calculated for $C_{32}H_{38}NO_2P$ 499.2640, found 499.2628.

270b: IR (neat) 3226, 3058, 2995, 2955, 2923, 2854, 1438, 1188, 1123 cm^{-1}; ^1H NMR (C_6D_6) δ 8.19-8.11 (m, 4 H), 7.29-7.26 (m, 2 H), 7.14-7.01 (m, 9 H), 4.56 (dd, *J* = 10.2, 7.9 Hz, 1 H), 3.26 (d, *J* = 5.2 Hz, 1 H), 2.98 (d, *J* = 15.9 Hz, 1 H), 2.28 (d, *J* = 5.2 Hz, 1 H), 2.09 (app q, *J* = 10.1 Hz, 1 H), 1.60 (d, *J* = 15.9 Hz, 1 H), 1.41-1.26 (m, 6 H), 1.16-1.10 (m, 1 H), 0.91 (t, *J* = 6.8 Hz, 3 H), 0.73-0.66 (m, 1 H), 0.65-0.57 (m, 1 H), 0.55-0.48 (m, 1 H), 0.31-0.19 (m, 3 H), 0.05 (dt, *J* = 8.3, 4.9 Hz, 1 H); ^{13}C NMR (C_6D_6) δ 141.70, 136.62, 135.99, 134.94, 134.29, 135.06, 132.94, 132.35, 132.23, 131.39, 131.35, 131.28, 131.25, 128.62, 128.45, 128.40, 127.51, 126.28, 61.80, 60.67, 54.10, 39.57, 34.13, 32.24, 24.05, 23.95, 23.40, 23.36, 23.07, 18.15, 14.44, 14.41, 12.04, 11.14; MS (EI) *m/z* (rel. intensity) 499 (M^+, 4), 481 (53), 326 (28), 218 (33), 201 (100); HRMS (EI) *m/z* calculated for $C_{32}H_{38}NO_2P$ 499.2640, found 499.2635.



271

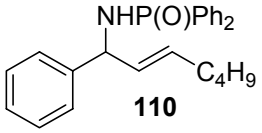
(4*S,7*S**)-4-((1*S**,2*S**)-2-Butylcyclopropyl)-5-(diphenylphosphinoyl)-7-phenyl-5-azaspiro-[2.5]octan-7-ol (271)**. To a suspension of NaH (14 mg, 0.35 mmol) in dry THF (1.0 mL) was added a solution of **270a** (35 mg, 0.070 mmol) in dry THF (0.40 mL) and HMPA (61 μL, 0.35 mmol). The reaction mixture was heated at 70 °C for 30 min, cooled to 0 °C, quenched with sat. NH_4Cl solution and extracted with EtOAc (3x). The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (7:3, hexanes/EtOAc containing 1% v/v Et_3N) to afford **271** (25 mg, 71%) as a colorless oil: IR (neat) 3331, 3059, 3003, 2954, 2923, 2852, 1439, 1179, 1120, 1105 cm^{-1}; ^1H NMR δ 8.01-7.94 (m, 2 H), 7.91-7.84 (m, 2 H), 7.60-7.56 (m, 2 H), 7.49-7.40 (m, 6 H), 7.35-7.32 (m, 2 H), 7.25-7.19 (m, 1 H), 6.21 (s, 1 H), 3.66 (dd, *J* = 22.1, 14.5 Hz, 1 H), 3.28-3.20 (m, 1 H), 2.86 (d, *J* = 14.0 Hz, 1 H), 1.67-1.39 (m, 6 H), 1.32-1.23 (m, 2 H), 1.11 (d, *J* = 14.0 Hz, 1 H), 1.01 (t, *J* = 7.0 Hz, 3 H), 0.86 (dt, *J* = 8.8, 5.6 Hz, 1 H), 0.61-0.52 (m, 2 H), 0.49-0.43 (m, 1 H), 0.35-0.28 (m, 1 H), 0.27-0.22 (m, 1 H), 0.20-0.14 (m, 1 H); ^{13}C NMR δ 145.42, 133.00, 132.88, 132.74, 132.62, 132.18, 132.06, 132.02, 131.94, 131.91, 131.02, 130.39, 129.32, 128.82, 128.65, 128.51, 128.34, 128.01, 126.78, 125.28, 71.18, 64.53, 52.99, 42.63, 34.20, 32.53, 22.77, 19.49, 19.37, 19.07, 16.98, 14.22, 13.89, 13.12, 8.93; MS (EI) *m/z* (rel. intensity) 499 (M^+, 15), 481 (23), 230 (32), 201 (100); HRMS (EI) *m/z* calculated for $C_{32}H_{38}NO_2P$ 499.2640, found 499.2637.



272

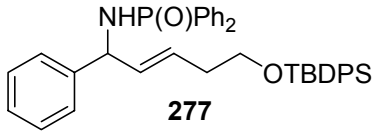
[(4*S,6*S**)-4-((1*S**,2*S**)-2-Butylcyclopropyl)-5-(diphenylphosphinoyl)-6-phenyl-5-azaspiro-[2.4]hept-6-yl]methanol (272)**. To a suspension of NaH (18 mg, 0.45 mmol) in dry THF (1.3 mL) was added a solution of **270b** (45 mg, 0.090 mmol) in dry THF (0.50 mL) and HMPA (78 μL, 0.45 mmol). The reaction mixture was heated at 70 °C for 30 min, cooled to 0 °C, quenched with sat. NH_4Cl solution and extracted with EtOAc (3x). The combined organic layers were

washed with H_2O and brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (1:1, hexanes/EtOAc containing 1% v/v Et_3N) to afford **270b** (34 mg, 75%) as a colorless oil: IR (neat) 3289, 3058, 3000, 2954, 2925, 2855, 1438, 1184, 1119, 1105 cm^{-1}; ^1H NMR δ 7.83-7.74 (m, 4 H), 7.50-7.35 (m, 9 H), 7.26-7.19 (m, 2 H), 3.50 (d, *J* = 7.3 Hz, 2 H), 3.02 (b, 1 H), 2.36 (dd, *J* = 9.3, 8.1 Hz, 1 H), 2.13-1.96 (m, 2 H), 1.45-1.34 (m, 1 H), 1.26-1.12 (m, 4 H), 0.96-0.90 (m, 1 H), 0.85 (t, *J* = 6.7 Hz, 3 H), 0.80-0.74 (m, 1 H), 0.62-0.55 (m, 2 H), 0.53-0.45 (m, 2 H), 0.28 (app t, *J* = 6.4 Hz, 2 H), 0.14-0.07 (m, 1 H); ^{13}C NMR δ 145.30, 134.27, 133.89, 132.82, 132.70, 132.58, 132.46, 132.20, 131.51, 131.48, 131.40, 131.37, 128.32, 128.24, 128.15, 128.07, 128.03, 127.20, 125.70, 72.24, 72.16, 67.01, 55.23, 45.73, 32.83, 31.30, 22.50, 20.60, 20.52, 18.73, 18.13, 14.07, 13.30, 11.96, 9.64; MS (EI) *m/z* (rel. intensity) 499 (M^+, 13), 481 (19), 230 (31), 201 (100); HRMS (EI) *m/z* calculated for $C_{32}H_{36}NOP$ (M-H_2O) 481.2535, found 481.2525.



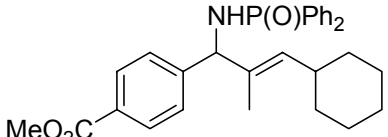
110

(*E*)-*N*-(1-Phenylhept-2-enyl)-*P*,*P*-diphenylphosphinamide (110).[133] **General Protocol K**. To a suspension of Cp_2ZrHCl (0.13 g, 0.49 mmol) in dry toluene (2.0 mL) was added **108** (60 μL, 0.52 mmol). The reaction mixture was heated in the microwave reactor (60 °C, 150 W) for 5 min, cooled to –78 °C, treated with Me_2Zn (0.16 mL, 0.33 mmol, 2.0 M in toluene), and warmed to 0 °C. After addition of **21** (0.10 g, 0.33 mmol), the mixture was heated in the microwave reactor (100 °C, 150 W) for 5 min, cooled to 0 °C, quenched with MeOH (0.25-0.50 mL), diluted with EtOAc, filtered through SiO_2 and concentrated. The residue was purified by chromatography on deactivated SiO_2 (3:7, hexanes/EtOAc containing 1% v/v Et_3N) to afford **110** (93 mg, 73%) as a colorless solid: ^1H NMR δ 7.97-7.90 (m, 2 H), 7.87-7.80 (m, 2 H), 7.53-7.21 (m, 11 H), 5.66 (ddt, *J* = 15.3, 6.2, 1.3 Hz, 1 H), 5.51 (dtd, *J* = 15.3, 6.4, 0.9 Hz, 1 H), 4.81 (td, *J* = 9.4, 6.4 Hz, 1 H), 3.25 (dd, *J* = 9.2, 6.1 Hz, 1 H), 1.99 (q, *J* = 6.2 Hz, 2 H), 1.31-1.26 (m, 4 H), 0.88 (t, *J* = 6.9 Hz, 3 H).



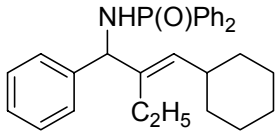
277

(*E*)-*N*-{5-[(tert-Butyldiphenylsilyl)oxy]-1-phenylpent-2-enyl}-*P*,P-diphenylphosphinamide (277).[163] According to the General Protocol K, Cp_2ZrHCl (0.13 g, 0.49 mmol), **125** (0.16 g, 0.52 mmol), Me_2Zn (0.16 mL, 0.33 mmol, 2.0 M in toluene) and **21** (0.10 g, 0.33 mmol) afforded **277** (0.12 g, 62%) as a colorless foam: ^{1}H NMR δ 7.94-7.79 (m, 4 H), 7.63 (d, *J* = 6.4 Hz, 4 H), 7.45-7.23 (m, 17 H), 5.74 (dd, *J* = 15.4, 6.0 Hz, 1 H), 5.52 (dt, *J* = 15.5, 6.5 Hz, 1 H), 4.85-4.76 (m, 1 H), 3.63 (t, *J* = 6.5 Hz, 2 H), 3.25-3.20 (m, 1 H), 2.26 (q, *J* = 6.5 Hz, 2 H), 1.01 (s, 9 H).



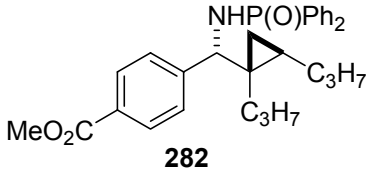
280

(*E*)-Methyl 4-(1-(*P*,*P*-diphenylphosphinoylamino)-3-cyclohexyl-2-methylallyl)benzoate (280). General Protocol L. To a suspension of Cp_2ZrHCl (0.14 g, 0.55 mmol) in dry toluene (1.5 mL) was added a freshly prepared solution of **279** (0.25 mL, 0.28 mmol, 1.1 M in toluene). The reaction mixture was heated in the microwave reactor (60 °C, 150 W) for 30 min, treated with **279** (0.25 mL, 0.28 mmol, 1.1 M in toluene), heated in the microwave reactor (60 °C) for 15 min, cooled to –78 °C, treated with Me_2Zn (0.14 mL, 0.28 mmol, 2.0 M in toluene), and warmed to 0 °C. After addition of **119** (0.10 g, 0.28 mmol), the solution was heated in the microwave reactor (100 °C, 150 W) for 5 min, cooled to 0 °C, quenched with MeOH (0.25-0.50 mL), diluted with EtOAc, filtered through SiO_2 and concentrated. The residue was purified by chromatography on deactivated SiO_2 (3:7, hexanes/EtOAc containing 1% v/v Et_3N) to afford **280** (81 mg, 60%) as a colorless foam: mp 147.0-148.6 °C (hexanes/EtOAc); IR (KBr) 3165, 3057, 2926, 2849, 1721, 1609, 1438, 1273, 1199, 1183, 1108 cm^{-1}; ^{1}H NMR δ 7.96-7.87 (m, 4 H), 7.85-7.77 (m, 2 H), 7.50-7.31 (m, 8 H), 5.24 (d, *J* = 9.1 Hz, 1 H), 4.71 (t, *J* = 10.7 Hz, 1 H), 3.88 (s, 3 H), 3.43 (dd, *J* = 10.5, 6.8 Hz, 1 H), 2.27-2.14 (m, 1 H), 1.73-1.62 (m, 5 H), 1.51 (d, *J* = 1.0 Hz, 3 H), 1.35-1.19 (m, 3 H), 1.15-0.98 (m, 2 H); ^{13}C NMR δ 166.83, 147.46, 147.40, 134.47, 133.38, 132.98, 132.61, 132.55, 132.47, 132.34, 131.94, 131.82, 131.68, 131.25, 129.61, 128.76, 128.42, 128.38, 128.26, 128.21, 127.02, 61.23, 51.95, 36.75, 32.83, 32.74, 25.91, 25.81, 13.30; MS (EI) *m/z* (intensity) 487 (M^+, 27), 404 (50), 364 (22), 286 (100), 218 (81), 201 (100); HRMS (EI) *m/z* calculated for $C_{30}H_{34}NO_3P$ 487.2276, found 487.2266.



278

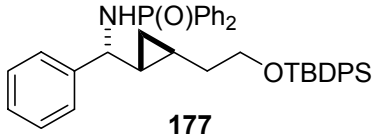
(*E*)-*N*-(3-Cyclohexyl-2-ethyl-1-phenylallyl)-*P*,*P*-diphenylphosphinamide (278). According to the General Protocol L, Cp_2ZrHCl (0.17 g, 0.66 mmol), **231** (89 mg, 0.66 mmol), Me_2Zn (0.16 mL, 0.33 mmol, 2.0 M in toluene) and **21** (0.10 g, 0.33 mmol) afforded **278** (91 mg, 63%) as a colorless solid: mp 135.5-137.2 °C (hexanes/EtOAc); IR (KBr) 3207, 3056, 2962, 2923, 2849, 1491, 1447, 1437, 1185, 1123, 1108 cm^{-1}; ^1H NMR δ 7.99-7.92 (m, 2 H), 7.89-7.82 (m, 2 H), 7.51-7.33 (m, 8 H), 7.31-7.18 (m, 3 H), 5.44 (d, *J* = 9.5 Hz, 1 H), 4.72 (t, *J* = 11.0 Hz, 1 H), 3.23 (dd, *J* = 10.2, 6.1 Hz, 1 H), 2.34-2.23 (m, 1 H), 2.17-2.05 (m, 1 H), 1.74-1.62 (m, 6 H), 1.37-1.07 (m, 5 H), 0.68 (t, *J* = 7.5 Hz, 3 H); ^{13}C NMR δ 142.57, 142.52, 139.39, 139.33, 133.70, 133.19, 132.82, 132.66, 132.53, 131.99, 131.86, 131.73, 131.69, 131.65, 131.45, 128.37, 128.30, 128.22, 128.13, 127.79, 127.53, 127.04, 58.74, 36.77, 33.44, 26.01, 25.95, 22.16, 13.92; MS (EI) *m/z* (intensity) 443 (M^+, 23), 360 (28), 306 (28), 242 (94), 218 (78), 201 (100); HRMS (EI) *m/z* calculated for $C_{29}H_{34}NOP$ 443.2378, found 443.2387.



282

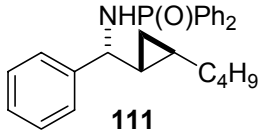
Methyl 4-[(*R)-(diphenylphosphinyl)amino((1*R**,2*R**)-1,2-dipropylcyclopropyl)-methyl]-benzoate (282). General Protocol M.** A microwave tube equipped with a rubber septa was flame-dried under vacuum and purged with N_2 upon cooling to r.t. The tube was charged with Cp_2ZrHCl (0.54 g, 2.1 mmol) and the solid was suspended in CH_2Cl_2 (3.0 mL). Upon addition of **281** (0.31 mL, 2.1 mmol) the reaction mixture was stirred for 20 min. The yellow-orange solution was cooled to –78 °C, treated sequentially with a solution of **119** (0.25 g, 0.70 mmol) in dry CH_2Cl_2 (0.5 mL) and Me_2Zn (1.0 mL, 2.1 mmol, 2.0 M in toluene) and warmed to 0 °C. The reaction mixture was heated in the microwave reactor (300 W, 100 °C) for 5 min and cooled to 0 °C. After treatment with CH_2I_2 (0.28 mL, 3.5 mmol), the mixture was heated in the microwave reactor (300 W, 60 °C) for 30 min, cooled to 0 °C, quenched with MeOH (ca. 0.50 mL), diluted with EtOAc (10 mL, 50 mL for washing), filtered through SiO_2 and concentrated. The residue was purified by chromatography on SiO_2 using the ISCO (0:1 to 1:0 hexanes/EtOAc, 40 g

column) to afford the desired amino cyclopropane **282** (0.21 g, 61%) as a colorless solid: mp 126.0-128.0 °C (hexanes/EtOAc); IR (KBr) 3195, 2956, 2930, 2871, 1722, 1610, 1437, 1277, 1183, 1108 cm^{-1}; ^1H NMR δ 7.94 (d, *J* = 8.2 Hz, 2 H), 7.83 (dd, *J* = 11.8, 6.9 Hz, 2 H), 7.68 (dd, *J* = 11.7, 7.3 Hz, 2 H), 7.53-7.38 (m, 4 H), 7.31-7.21 (m, 4 H), 4.19 (t, *J* = 10.4 Hz, 1 H), 3.92 (s, 3 H), 3.24 (dd, *J* = 9.7, 6.8 Hz, 1 H), 1.59-1.23 (m, 6 H), 1.16-1.03 (m, 3 H), 0.87 (t, *J* = 7.3 Hz, 3 H), 0.79 (t, *J* = 7.2 Hz, 3 H), 0.70-0.61 (m, 1 H), 0.01 (t, *J* = 5.0 Hz, 1 H); ^{13}C NMR δ 166.94, 147.81, 147.77, 132.43, 132.31, 131.94, 131.81, 131.71, 131.68, 129.37, 128.83, 128.55, 128.38, 128.27, 128.10, 127.23, 58.91, 51.98, 32.36, 31.06, 29.57, 29.51, 23.12, 21.91, 20.57, 15.09, 14.45, 14.09; MS (EI) *m/z* (intensity) 489 (M^+, 5), 364 (53), 298 (55), 288 (28), 218 (48), 201 (100); HRMS (EI) *m/z* calculated for $C_{30}H_{36}NO_3P$ 489.2433, found 489.2426.



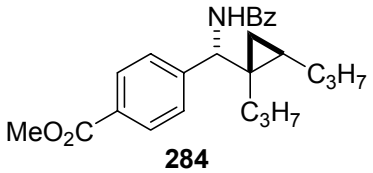
177

***N*-(*R**)-(((1*R**,2*S**)-2-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)cyclopropyl)(phenyl)methyl)-*P*,*P*-diphenylphosphinamide (177)**. According to the General Protocol M, Cp_2ZrHCl (0.63 g, 2.5 mmol), **125** (0.76 g, 2.5 mmol), Me_2Zn (1.2 mL, 2.5 mmol, 2.0 M in toluene), **21** (0.25 g, 0.82 mmol) and CH_2I_2 (0.33 mL, 4.1 mmol) afforded **177** (0.35 g, 68%) as a colorless foam.



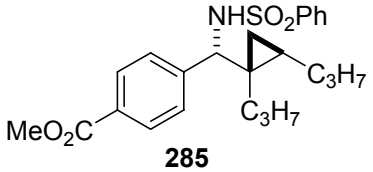
111

N-(*R)-(((1*R**,2*R**)-2-Butylcyclopropyl)(phenyl)methyl)-*P*,*P*-diphenylphosphinamide (111)**. According to the General Protocol M, Cp_2ZrHCl (0.63 g, 2.5 mmol), **108** (0.28 mL, 2.5 mmol), Me_2Zn (1.2 mL, 2.5 mmol, 2.0 M in toluene), **21** (0.25 g, 0.82 mmol), and CH_2I_2 (0.33 mL, 4.1 mmol) afforded **111** (0.20 g, 61%) as a colorless solid: ^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, *J* = 6.6 Hz, 1 H), 1.36-1.29 (m, 5 H), 1.10-0.98 (m, 2 H), 0.89 (t, *J* = 7.0 Hz, 3 H), 0.78-0.72 (m, 1 H), 0.41 (dt, *J* = 8.6, 4.8 Hz, 1 H), 0.26 (dt, *J* = 8.3, 5.0 Hz, 1 H).



284

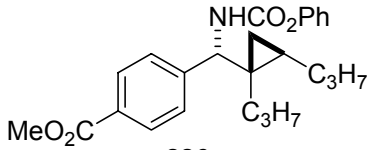
Methyl 4-[(*R)-benzoylamino((1*R**,2*R**)-1,2-dipropylcyclopropyl)methyl]benzoate (284).** To a solution of **282** (50 mg, 0.10 mmol) in dry MeOH (1.0 mL) was added a solution of HCl (1.0 mL, 4.0 M in MeOH). The reaction mixture was stirred for 12 h and concentrated to afford a colorless solid. The residue was dissolved in dry CH_2Cl_2 (1.0 mL), cooled to 0 °C and treated with DMAP (1.0 mg, 10 μmol), DIPEA (53 μL, 0.31 mmol) and BzCl (24 μL, 0.20 mmol). The mixture was warmed to r.t., stirred for 3 h and concentrated. The residue was purified by chromatography on SiO_2 (9:1, hexanes/EtOAc) to afford **284** (40 mg, 100%) as a colorless oil: IR (neat) 3303, 2955, 2930, 2871, 1725, 1635, 1528, 1280, 1110 cm^{-1}; ^1H NMR δ 8.01-7.74 (m, 2 H), 7.81-7.78 (m, 2 H), 7.56-7.43 (m, 3 H), 7.39 (d, *J* = 8.2 Hz, 2 H), 6.52 (d, *J* = 7.8 Hz, 1 H), 5.19 (d, *J* = 7.9 Hz, 1 H), 3.91 (s, 3 H), 1.56-1.33 (m, 6 H), 1.27-1.16 (m, 2 H), 0.91 (t, J = 7.1 Hz, 3 H), 0.84 (t, *J* = 6.9 Hz, 3 H), 0.80-0.71 (m, 2 H), 0.14 (t, *J* = 4.9 Hz, 1 H); ^{13}C NMR δ 166.86, 166.67, 145.76, 134.33, 131.63, 129.64, 129.03, 128.66, 126.98, 126.85, 58.02, 52.02, 32.92, 30.94, 27.76, 23.14, 21.69, 20.82, 15.65, 14.59, 14.08; MS (EI) *m/z* (intensity) 393 (M^+, 8), 350 (18), 322 (27), 202 (52), 105 (100); HRMS (EI) *m/z* calculated for $C_{25}H_{31}NO_3$ 393.2304, found 393.2314.



285

Methyl 4-[(*R)-benzenesulfonylamino ((1*R**,2*R**)-1,2-dipropylcyclopropyl)methyl]-benzoate (285).** To a solution of **282** (50 mg, 0.10 mmol) in dry MeOH (1.0 mL) was added a solution of HCl (1.0 mL, 4.0 M in MeOH). The reaction mixture was stirred for 12 h and concentrated to afford a colorless solid. The residue was dissolved in dry CH_2Cl_2 (1.0 mL), cooled to 0 °C and treated with DMAP (1.0 mg, 10 μmol), DIPEA (53 μL, 0.31 mmol) and $PhSO_2Cl$ (26 μL, 0.20 mmol). The mixture was warmed to r.t., stirred for 3 h and concentrated. The residue was purified by chromatography on SiO_2 (9:1, hexanes/EtOAc) to afford **285** (43 mg, 98%) as a colorless oil: IR (neat) 3281, 2956, 2871, 1724, 1612, 1448, 1436, 1327, 1281, 1163, 1111 cm^{-1}; ^1H NMR δ 7.80 (d, *J* = 8.4 Hz, 2 H), 7.71-7.67 (m, 2 H), 7.49-7.44 (m, 1 H),

7.37-7.31 (m, 2 H), 7.08 (d, J = 8.2 Hz, 2 H), 5.32 (d, J = 7.3 Hz, 1 H), 4.32 (d, J = 7.3 Hz, 1 H), 3.89 (s, 3 H), 1.42-1.12 (m, 6 H), 1.09-0.95 (m, 3 H), 0.82 (t, J = 7.2 Hz, 3 H), 0.72 (t, J = 7.0 Hz, 3 H), 0.46-0.36 (m, 1 H), -0.02 (t, J = 5.4 Hz, 1 H); ^{13}C NMR δ 166.75, 144.48, 140.14, 132.44, 129.29, 128.95, 128.76, 127.06, 126.97, 61.68, 52.06, 32.32, 30.72, 28.48, 22.98, 21.60, 20.39, 14.99, 14.36, 14.00; MS (EI) *m/z* (intensity) 429 (M^+, 11), 304 (100), 272 (45), 229 (46), 212 (61), 141 (55), 132 (42); HRMS (EI) *m/z* calculated for $C_{27}H_{27}NO_4S$ 429.1974, found 429.1955.



286

Methyl 4-[(1*R,2*R**)-1,2-dipropylcyclopropyl-((*R**)-phenoxycarbonylaminomethyl)]-benzoate (286).** To a solution of **282** (50 mg, 0.10 mmol) in dry MeOH (1.0 mL) was added a solution of HCl (1.0 mL, 4.0 M in MeOH). The reaction mixture was stirred for 12 h and concentrated to afford a colorless solid. The residue was dissolved in dry CH_2Cl_2 (1.0 mL), cooled to 0 °C and treated with DMAP (1.0 mg, 10 μmol), DIPEA (53 μL, 0.31 mmol) and $ClCO_2Ph$ (26 μL, 0.20 mmol). The mixture was warmed to r.t., stirred for 3 h and concentrated. The residue was purified by chromatography on SiO_2 (9:1, hexanes/EtOAc) to afford **286** (39 mg, 94%) as a colorless solid: mp 140.0-141.5 °C (hexanes/EtOAc); IR (neat) 3317, 3005, 2955, 2933, 2871, 1713, 1611, 1520, 1491, 1468, 1456, 1433, 1282, 1204, 1116 cm^{-1}; ^{1}H NMR δ 8.03 (d, J = 8.2 Hz, 2 H), 7.38 (d, J = 8.3 Hz, 2 H), 7.38-7.32 (m, 2 H), 7.21-7.11 (m, 3 H), 5.46 (d, J = 8.1 Hz, 1 H), 4.83 (d, J = 8.1 Hz, 1 H), 3.93 (s, 3 H), 1.65-1.10 (m, 8 H), 0.93 (t, J = 7.2 Hz, 3 H), 0.85 (t, J = 6.8 Hz, 3 H), 0.78-0.62 (m, 2 H), 0.11 (t, J = 4.8 Hz, 1 H); ^{13}C NMR δ 166.84, 154.00, 150.88, 129.64, 129.21, 129.14, 126.94, 125.28, 121.42, 59.33, 52.08, 32.66, 30.87, 27.71, 23.09, 21.54, 20.62, 15.19, 14.52, 14.08; MS (EI) *m/z* (intensity) 409 (M^+, 3), 284 (58), 273 (54), 218 (100), 191 (47), 94 (81); HRMS (EI) *m/z* calculated for $C_{25}H_{31}NO_4$ 409.2253, found 409.2271.

2.0 Synthesis and Structural Evaluation of Cyclopropyl Peptide Mimetics

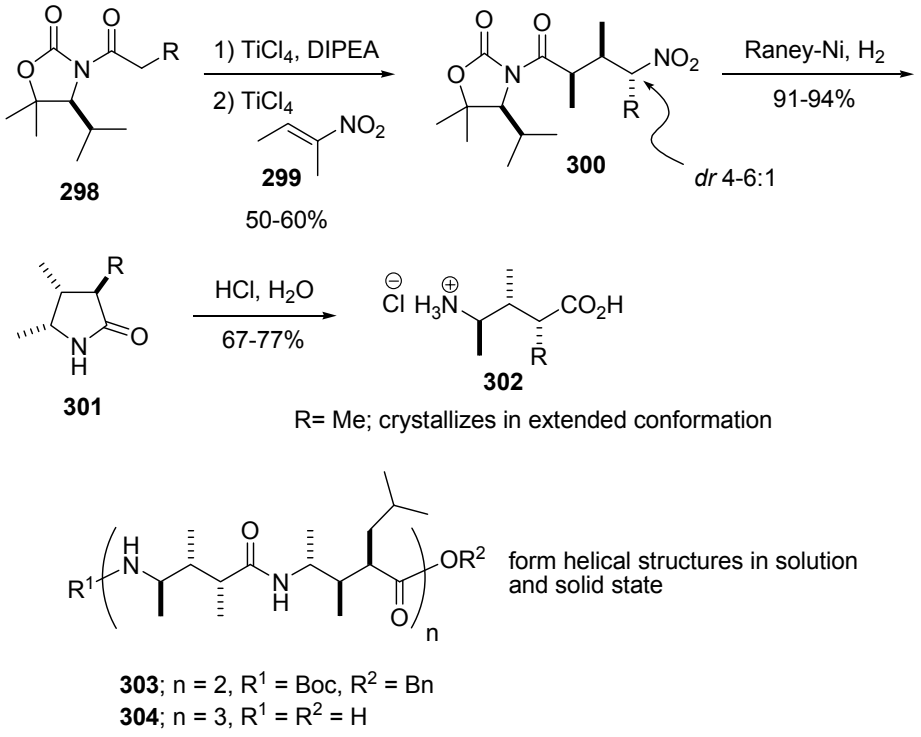
2.1 Introduction

2.1.1 Foldamers

Peptides are the natural ligands for various enzymes and have been found to exhibit broad physiological effects. However, they are not useful drug substances since they often suffer from poor bioavailability and transport through membranes and have very short half-lives due to degradation by peptidases. Modification of native peptide sequences is a promising avenue for the development of novel pharmaceuticals to circumvent some of these issues, the majority of which target the scissile peptide bond. The favorable interactions of native peptides with proteins are due in large part to their ability to adopt complementary secondary structures to enhance binding. In recent years, the structural motifs of β- and γ-amino acids[233] have been studied extensively and with greater understanding of their unique folding properties coupled with the power of chemical genetics,[234] the structure based design[235] of new therapeutic agents is possible. Much like their natural counterparts, β- and γ-amino acids have been found to form a variety of helical and pleated sheet-like structural motifs. One of the most intriguing aspects of β- and γ-amino acids is the increased structural diversity that can be attained since more sp^3-carbons are present in the peptide backbone. For example, Seebach and co-workers have recently described the synthesis and structural properties of a series of substituted γ-amino acid derivatives.[236] A diasteroselective conjugate addition of acyloxazolidinone **298** to nitroalkene **299** affords a mixture of α-NO_2 diastereomers. Hydrogenation and acidic opening of lactam **301** gave the hydrochloride salt **302** which crystallizes in an extended conformation forming long stacks of parallel sheet-like structures. Conversely, tetrapeptide **303** forms a helical structure

[233] For some recent reviews on β- and γ-amino acids, see (a) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015. (b) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219. (c) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893.
[234] Stockwell, B. R. *Nat. Rev. Gen.* **2000**, *1*, 116.
[235] Anderson, A. C. *Chem. Biol.* **2003**, *10*, 787.
[236] Seebach, D.; Brenner, M.; Rueping, M.; Jaun, B. *Chem. Eur. J.* **2002**, *8*, 573.

(2.6_{14} helix)[237] in the solid state, and NMR studies of the related hexapeptide **304** found a conformational preference for a family of helical structures.



Scheme 2.1. γ-Amino acids can adopt both extended and helical structures

A new family of γ-amino acid derivatives was reported by Schreiber and Clardy in 1992. The vinylogous amino acids **307** were designed on the basis of allylic strain to favor the formation of extended structures (Figure 2.1).[238] The protected building blocks were easily prepared from the corresponding α-amino acid derivatives via reduction and homologation using a Horner-Wadsworth-Emmons olefination. Under standard coupling conditions, oligopeptides such as **369** (a vinylogous dipeptide) were prepared and found to form extended, sheet-like structures in the solid state. One of the major drawbacks of the use of these derivatives is the reactivity of the alkene towards conjugate additions, and a β-methoxy-γ-amino acid was formed during saponification of an amino ester in methanol. In fact, this undesired side reaction became

[237] The notation n_m is used to describe helical structures where n represents the number of residues per helical turn and m is the number of atoms involved in the ring containing the hydrogen bond. For example, the traditional α-helix can also be called a 3.6_{14} helix. Voet, D.; Voet, J. G., *Biochemistry, 2nd Ed.*; John Wiley & Sons, Inc.: New York, 1995; p 146.
[238] Hagihara, M.; Anthony, N. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6568.

a fortuitous discovery as the incorporation of this amino acid into a tetrapeptide resulted in the formation of a novel helical structure in both the solid state and in solution.

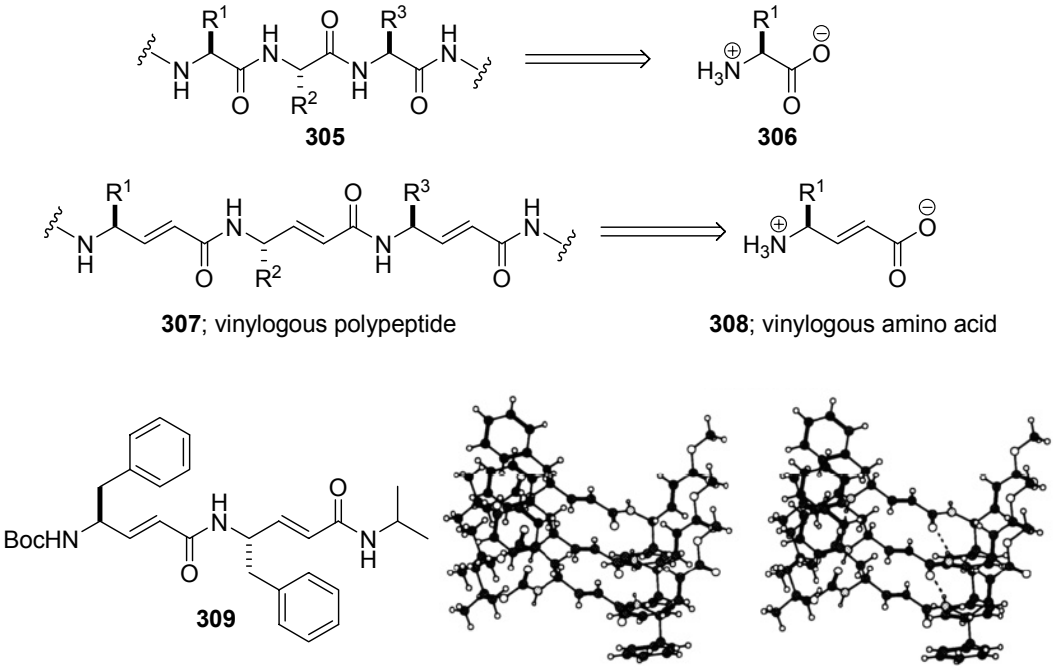


Figure 2.1. Schreiber's vinylogous polypeptides as β-sheet mimetics

2.1.2 Peptidomimetics

An alternate approach to the problems associated with native peptides is the isosteric replacement of the peptide bond. A number of these peptide isosteres[239] have been designed to maintain the excellent binding capabilities of peptides, but replace the amide bond with a rigid, hydrolytically stable moiety (Figure 2.2).[240] Some of the most commonly used amide bond isosteres include the ketomethylene, hydroxyethylene, dihydroxyethylene, hydroxyethylamino and *E*-alkene peptide isosteres. A number of these isosteric replacements function as transition state analogs for the hydrolysis of the peptide bond. Short peptides incorporating hydroxyethylene or hydroxymethylene isosteres, such as Indinavir, have found use as inhibitors of proteases, such as HIV-I.[241]

[239] (a) Horwell, D. C. *Biorg. Med. Chem.* **1996**, *4*, 1573. (b) Venkatesan, N.; Kim, B. H. *Curr. Med. Chem.* **2002**, *9*, 2243.
[240] Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789.
[241] Bursavich, M. G.; Rich, D. H. *J. Med. Chem.* **2002**, *45*, 541 and references therein.

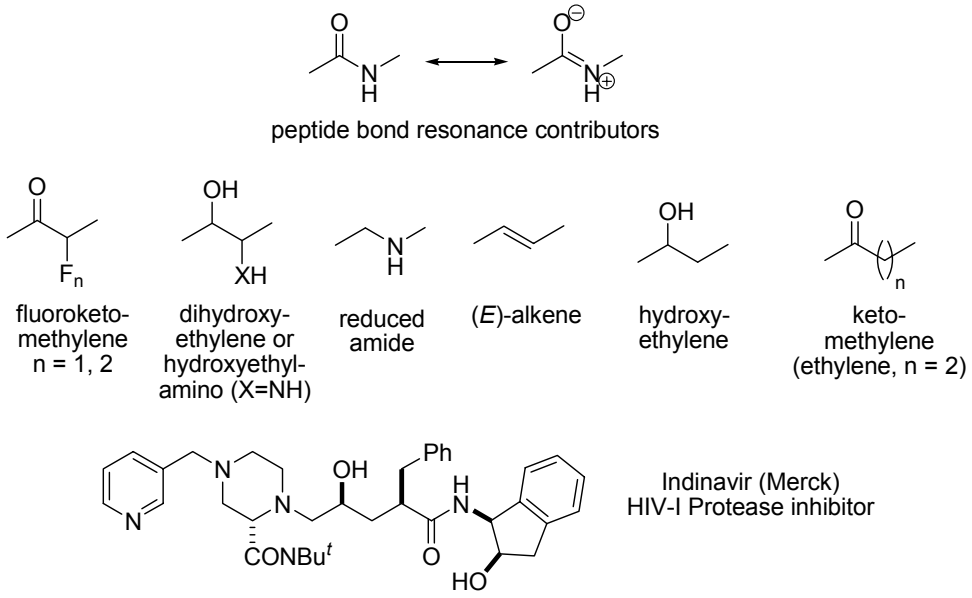
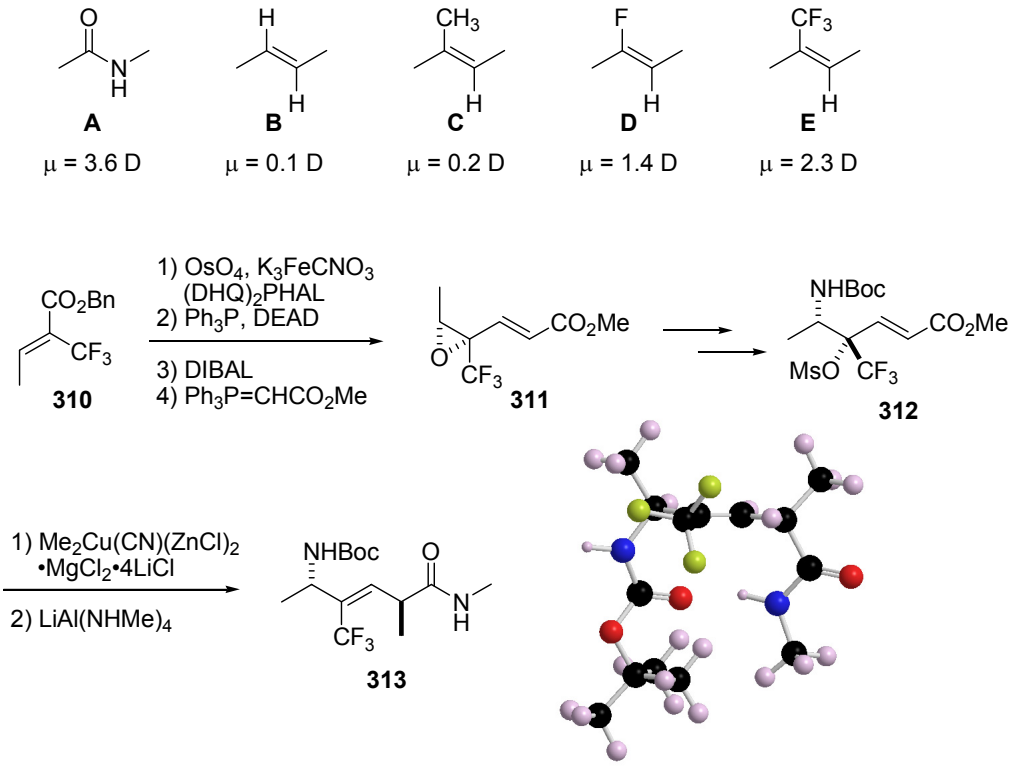


Figure 2.2. The peptide bond and representative isosteres

(*E*)-Alkene peptide isosteres (EAPIs) are closely related to the cyclopropyl peptide mimics that we have prepared and most accurately mimic the amide bond in terms of geometry, rigidity, bond angle and length, but lack hydrogen bonding capability. EAPIs have been found to be particularly effective in promoting β-turns and in initiating β-hairpin motifs.[242,243] Most peptide isosteres shown in Figure 2.2 fail to account for the resonance contribution of the zwitterionic form of the amide bond which imparts both rigidity to the peptide backbone and significant dipole moment (μ) to the amide bond. In an effort to incorporate a mimic for the dipole moment into an EAPI, Wipf and Henninger reported the synthesis and evaluation of trifluoromethyl-substituted (*E*)-alkenes as β-turn mimetics (Scheme 2.2).[244] Of the alkene isosteres prepared to date, a CF_3-substituted alkene most accurately mimics the dipole moment of the amide bond (2.3 D vs. 3.6 D). The intermediate epoxide **311** is prepared in 4 steps from enoate **310** via a Sharpless asymmetric dihyroxylation[245] followed by a Mitsunobu reaction[246] to

[242] (a) Gardner, R. R.; Liang, G.-B.; Gellman, S. H. *J. Am. Chem. Soc.* **1995**, *117*, 3280.
[243] (a) Wipf, P.; Henninger, T. C. *J. Org. Chem.* **1997**, *62*, 1586. (b) Wipf, P.; Henninger, T. C.; Geib, S. J. *J. Org. Chem.* **1998**, *63*, 6088.
[244] Wipf and Xiao have recently applied the Zr→Zn methodologies developed in Chapter 1 to the preparation of a library of substituted trisubstituted (*E*)-alkene peptide isosteres for evaluation as β-turn mimics and structural replacements of a dipeptide segment of the antibiotic Gramicidin S.
[245] Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
[246] Mitsunobu, O. *Synthesis* **1981**, 1.

form the epoxide, reduction and chain homologation with a stabilized Wittig reagent. Azide opening of the epoxide, Staudinger reduction and *N*-protection followed by activation of the 3° alcohol afforded the allylic mesylate **312**. Allylic displacement of the mesylate with the mixed cuprate reagent followed by amidation afforded the dipeptide isostere of *L*-Ala-*D*-Ala. Indeed, in the solid state, **313** and the corresponding methyl-substituted alkene peptide isostere fold into very similar stable type II β-turns. Interestingly, the use of an (*E*)-disubstituted alkene resulted in a more extended structure.

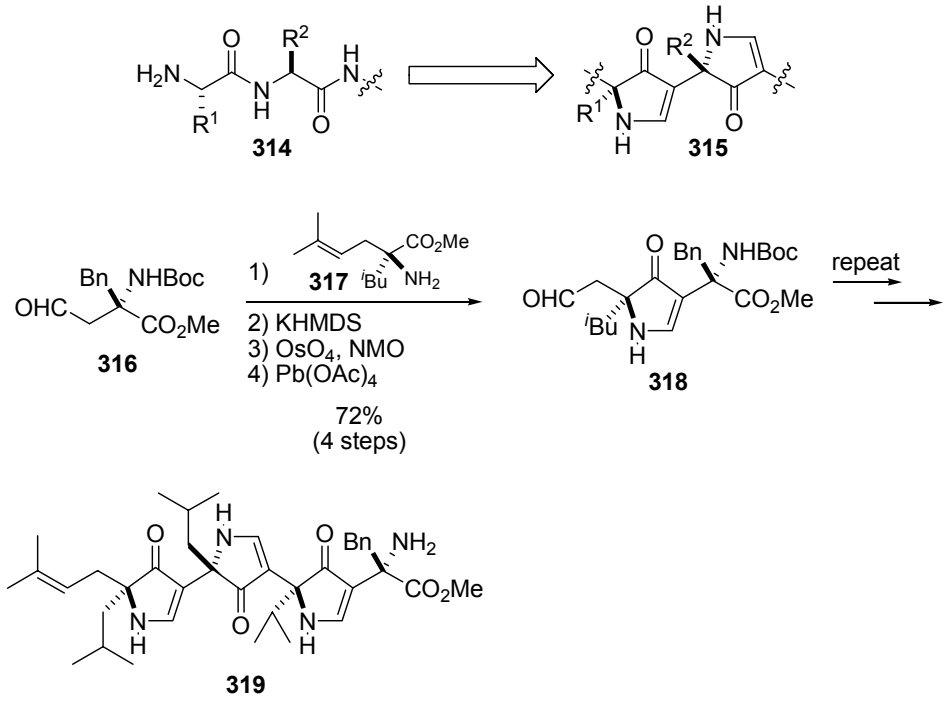


Scheme 2.2. Synthesis and crystal structure of a CF_3-substituted (*E*)-alkene dipeptide isostere of *L*-Ala-*D*-Ala as a β-turn mimetic

There have been numerous systems designed to mimic α-helices or β-turn motifs, however, there have been far fewer studies on β-sheet mimetics.[247] Unlike helical or turn motifs,

[247] For selected examples of β-sheet mimics, see (a) Diaz, H.; Tsang, K. Y.; Choo, D.; Espina, J. R.; Kelly, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 3790. (b) Chen, L.; Trilles, R. V.; Tilley, J. W. *Tetrahedron Lett.* **1995**, *36*, 8715. (c) Boumendjel, A.; Roberts, J. C.; Hu, E.; Pallai, P. V.; Rebek, Jr., J. *J. Org. Chem.* **1996**, *61*, 4434. (d) Seebach, D.; Abele, S.; Gademann, K.; Jaun, B. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1595. (e) Nowick, J. S.; Lam, K. S.; Khasanova, T. V.; Kemnitzer, W. E.; Maitra, S.; Mee, H. T.; Liu, R. *J. Am. Chem. Soc.* **2002**, *124*, 4972.

extended structures can not be readily characterized using NMR techniques and the reliance upon x-ray crystallography raises issues of whether the structure arises solely from favorable packing interactions in the solid state or a genuine conformational preference. On the basis of preliminary molecular modeling, Smith and co-workers developed pyrrolidinone scaffolds to mimic the extended conformation of β-sheets.[248] Indeed, the minimum energy conformation of an oligopyrrolidinone scaffold in an extended conformation[249] was found to overlay extremely well with the crystal structure of the corresponding α-peptide. Synthetically, the α,α-disubstituted amino acid **316** was prepared using Seebach's self-regeneration of stereocenters methodology and was subjected to an iterative protocol for the preparation of oligopyrrolidinone **319**. Formation of the Schiff base of **316** with amine **317** followed by cyclization with KHMDS, and oxidative cleavage of the isoprenyl olefin afforded aldehyde **318**. Repetition of this protocol afforded the tetrapeptide mimic **319**. They observed excellent correlation of the x-ray structure of **319** with its α-peptide analog.



Scheme 2.3. Smith and co-worker's scaffold for mimicking β-sheets formed by α-peptides

[248] Smith, III, A. B.; Guzman, M. C.; Sprengeler, P. A.; Keenan, T. P.; Holcomb, R. C.; Wood, J. L.; Carroll, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1994**, *116*, 9947.
[249] Three families of conformations were found, including "linear", "turned" and "twisted" conformations.

2.1.3 Cyclopropyl Amino Acids and Peptide Isosteres

While there are not many examples of naturally occurring amino acids containing alkenes, a number of naturally occurring cyclopropane-containing amino acids and peptides have been isolated (Figure 2.3).[250] The most common are the 2,3-methanoamino acids where a cyclopropane has been inserted between the α- and β- positions of an α-amino acid. For example, the most common cyclopropyl amino acid, Acc, could also be called 2,3-methanoalanine (Figure 2.3). The conformational preferences of 2,3-methanoamino acids have been studied by Burgess and co-workers using a combination of computational and experimental techniques.[251] The local conformational preference of the constituent amino acid residues of cyclopropyl peptides can be more easily rationalized than the overall secondary structures. However, the *de novo* prediction of secondary structures should prove to be considerably more facile for the conformationally constrained cyclopropyl amino acids than for the corresponding α-amino acids.

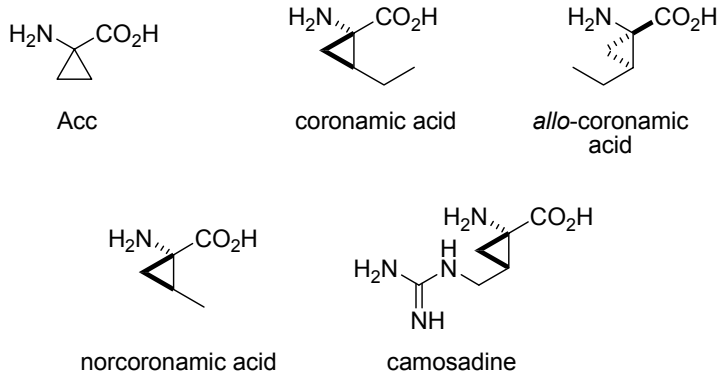
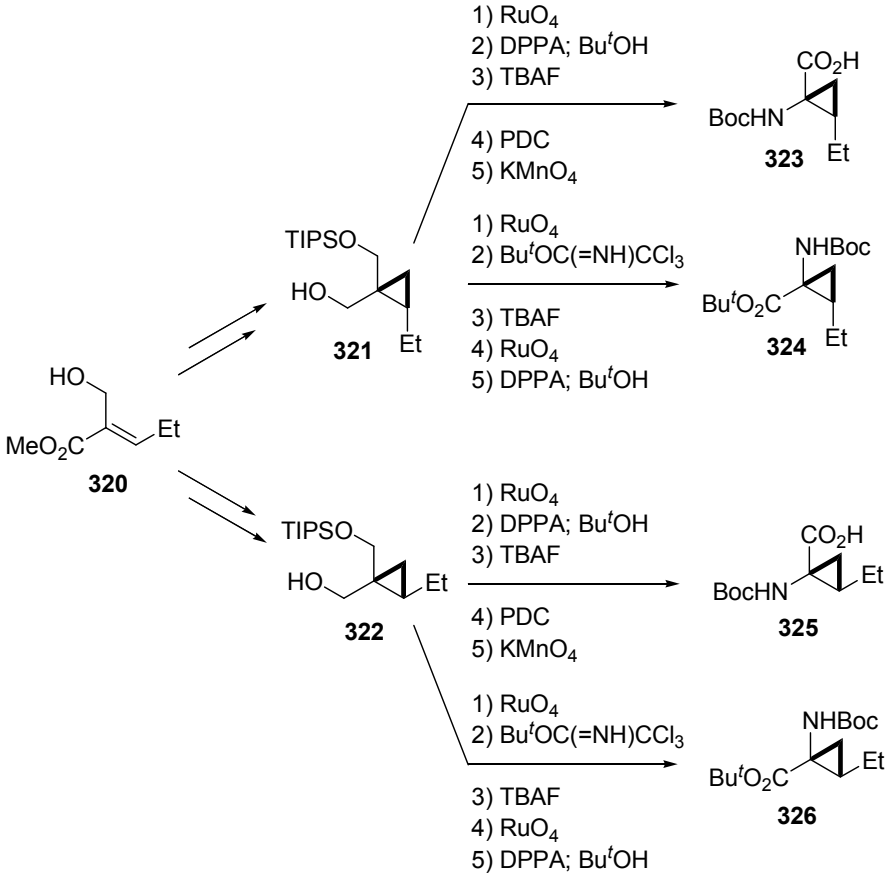


Figure 2.3. Some naturally occurring cyclopropane-containing amino acids

There have been many examples of syntheses of cyclopropane-containing amino acids via alkylation,[252] conjugate addition,[253] or diazoester chemistry.[254] Charette and Côté have

[250] For reviews on cyclopropane-containing amino acids, see (a) Stammer, C. H. *Tetrahedron* **1990**, *46*, 2231. (b) Burgess, K.; Ho, K.-K.; Moye-Sherman, D. *Synlett* **1994**, 575. (c) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603.
[251] (a) Burgess, K.; Ho, K.-K. *J. Org. Chem.* **1992**, *57*, 5931. (b) Burgess, K.; Ho, K.-K. *Tetrahedron Lett.* **1992**, *33*, 5677. (c) Burgess, K.; Ho, K.-K.; Ke, C.-Y. *J. Org. Chem.* **1993**, *58*, 3767. (d) Burgess, K.; Lim, D.; Ho, K.-K.; Ke, C.-Y. *J. Org. Chem.* **1994**, *59*, 2179.
[252] Groth, U.; Halfbrodt, W.; Schollkopf, U. *Liebigs Ann. Chem.* **1992**, 351.
[253] (a) Williams, R. M.; Fegley, G. J. *J. Am. Chem. Soc.* **1991**, *113*, 8796. (b) Williams, R. M.; Fegley, G. J. *J. Org. Chem.* **1993**, *58*, 6933.
[254] Davies, H. L. M.; Hutcheson, D. K. *Tetrahedron Lett.* **1993**, *34*, 7243.

recently reported a nice application of their asymmetric cyclopropanation methodology to the synthesis of all stereoisomers of coronamic acid (Scheme 2.4).[255]



Scheme 2.4. Synthesis of all four isomers of coronamic acid: Charette's general approach to 2,3-methanoamino acids

Starting from allylic alcohol **320**, protective group manipulations and asymmetric cyclopropanation affords the cyclopropylmethanols **321** and **322**. Depending upon the ordering of the subsequent oxidation and deprotection steps, (+)- and (-)-coronamic acid derivatives, **323** and **324**, and (+)- and (-)-*allo*-coronamic acid derivatives, **325** and **326**, can be prepared from **321** and **322** in 5 chemical steps. This diversity-oriented approach to the preparation of cyclopropyl amino acids could be easily expanded to the generation of an impressive library of analogs for biological evaluation or incorporation into known biologically active peptide sequences.

[255] Charette, A. B.; Côté, B. *J. Am. Chem. Soc.* **1995**, *117*, 12721.

Martin and co-workers have been interested in the insertion of conformationally restricted cyclopropyl amino acids into biologically relevant peptide sequences in the hope to increase both the stability of the peptide and its binding affinity (Figure 2.4).[256] Interestingly, they have not only chosen to rigidify the peptide backbone, but have also attempted to mimic the side chain position of the residue which has been replaced.[256d] At the outset of their studies, it was not known whether **327** was bound to its target (in this case, Ras farnesyltransferase) in an extended or folded conformation. They introduced both *cis*- and *trans*-trisubstituted cyclopropyl peptide isosteres in order to account for each binding possibility along with the hydroxyethylene isostere **331** as a control element. Unfortunately, the introduction of all three isosteres appears to have deleterious effects on the bioactivity of the peptides compared to the native ligand **327** (38 nM). It may be more instructional to test libraries of cyclopropyl peptide mimetics against a variety of biological targets rather than attempting to 'rationally design' a peptide-like inhibitor by modifiying the constituent amino acids. Considerable synthetic effort was required to prepare the required cyclopropyl amino acid residues (9-10 steps) and it stands to reason that using this design principle, one would prefer to choose a target such that the binding mode of the native peptide is well understood.

[256] (a) Martin, S. F.; Austin, R. E.; Oalmann, C. J. *Tetrahedron Lett.* **1990**, *31*, 4731. (b) Martin, S. F.; Oalmann, C. J.; Liras, S. *Tetrahedron* **1993**, *49*, 3521. (c) Martin, S. F.; Dwyer, M. P.; Hartmann, B.; Knight, K. S. *J. Org. Chem.* **2000**, *65*, 1305. (d) Hillier, M. C.; Davidson, J. P.; Martin, S. F. *J. Org. Chem.* **2001**, *66*, 1657. (e) Davidson, J. P.; Lubman, O.; Rose, T.; Waksman, G.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 205. (f) Reichelt, A.; Gaul, C.; Frey, R. R.; Kennedy, A.; Martin, S. F. *J. Org. Chem.* **2002**, *67*, 4062. (g) Franklin, C. L.; Li, H.; Martin, S. F. *J. Org. Chem.* **2003**, *68*, 7298. (h) Plake, H. R.; Sundberg, T. H.; Woodward, A. R.; Martin, S. F. *Tetrahedron Lett.* **2003**, *44*, 1571.

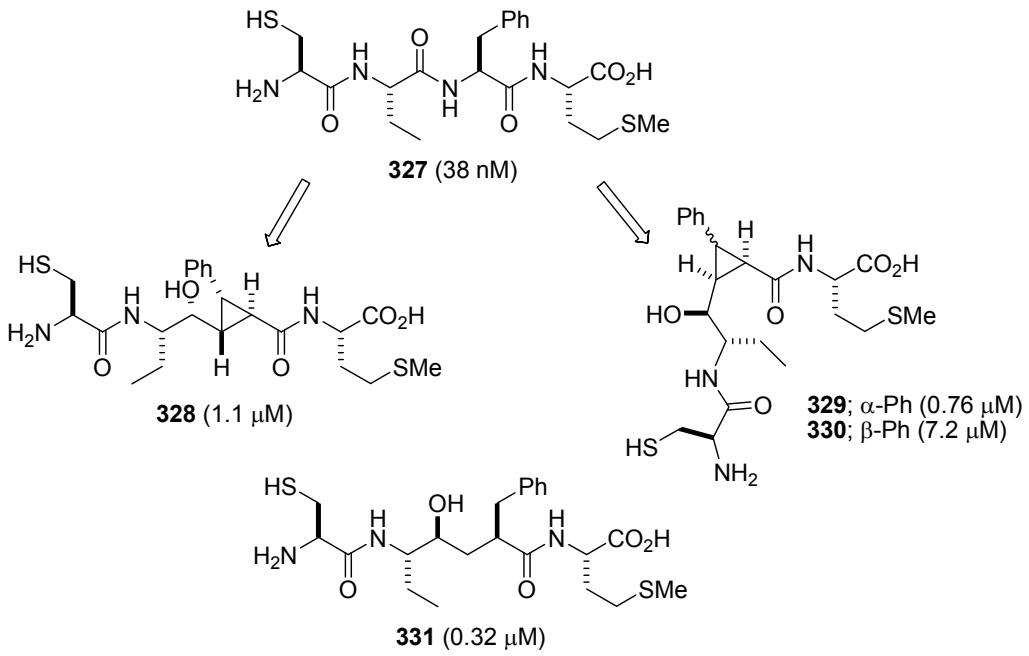


Figure 2.4. Martin's cyclopropane-derived peptidomimetics as Ras farnesyltransferase inhibitors

2.2 Synthetic Approaches to α,β-Cyclopropl-γ-Amino Acids

There have been many attempts to use amide bond isosteres as potential therapeutic agents, however limited success has been achieved. A selection of the numerous methods available for the preparation of structurally diverse peptides and peptide mimetics was highlighted in the introduction for this chapter. Some of the most interesting examples, in terms of medicinal potential, arise from the preparation of novel amino acid scaffolds which are capable of adopting stable folded structures. With methodology in place for the stereoselective synthesis of *C*-cyclopropylalkylamides (see Chapter 1.3.1), we wanted to utilize this process for the preparation of novel amino acid scaffolds for potential use as β-sheet mimics. As shown in the introductory section, there has been widespread use of alkenes as replacements for the scissile peptide bond. One of the major disadvantages of olefins is their inherent reactivity[257] along with possibilities for isomerization and allylic oxidation. On the other hand, cyclopropanes maintain the rigidity of the peptide backbone but are inherently less reactive under the conditions employed in traditional peptide synthesis. We hypothesized that the incorporation of a cyclopropyl spacer in α-amino acids would confer structural rigidity into the peptide backbone (as was observed for Schreiber's vinylogous amino acids) while significantly decreasing the reactivity of the subunits during oligopeptide synthesis. In order to test our hypothesis, we set out to prepare a small family of di- and tri-substituted cyclopropyl amino acids and survey the effect of substitution on the conformation of simple amide derivatives (Figure 2.5). On the basis of minimization of $A^{1,3}$-strain arguments (arrows indicate minimized interactions), the *syn*-cyclopropyl amino amide **336** should adopt the most extended structure. The substitution of R^3=Me will re-enforce this conformation in order to minimize interactions across the cyclopropane. Using the same arguments for the *anti*-diastereomer **337**, we can envisage that these compounds will also adopt an extended structure based on allylic strain. However, the relative stereochemistry appears to impose a turn about the N-C1-C2-C3 dihedral angle. The introduction of a β-methyl substituent

[257] This disadvantage is nicely displayed in the work of Schreiber and co-workers where methanol added in a 1,4 fashion to their designed amino acid during ester saponification. See reference 238 for details.

(ie, $^{\beta}$MeΔPhg) will introduce significant $A^{1,2}$-strain in conformer **337**, potentially resulting in a twist back to a more extended structure (ie, a clockwise rotation about C1-C2).[258]

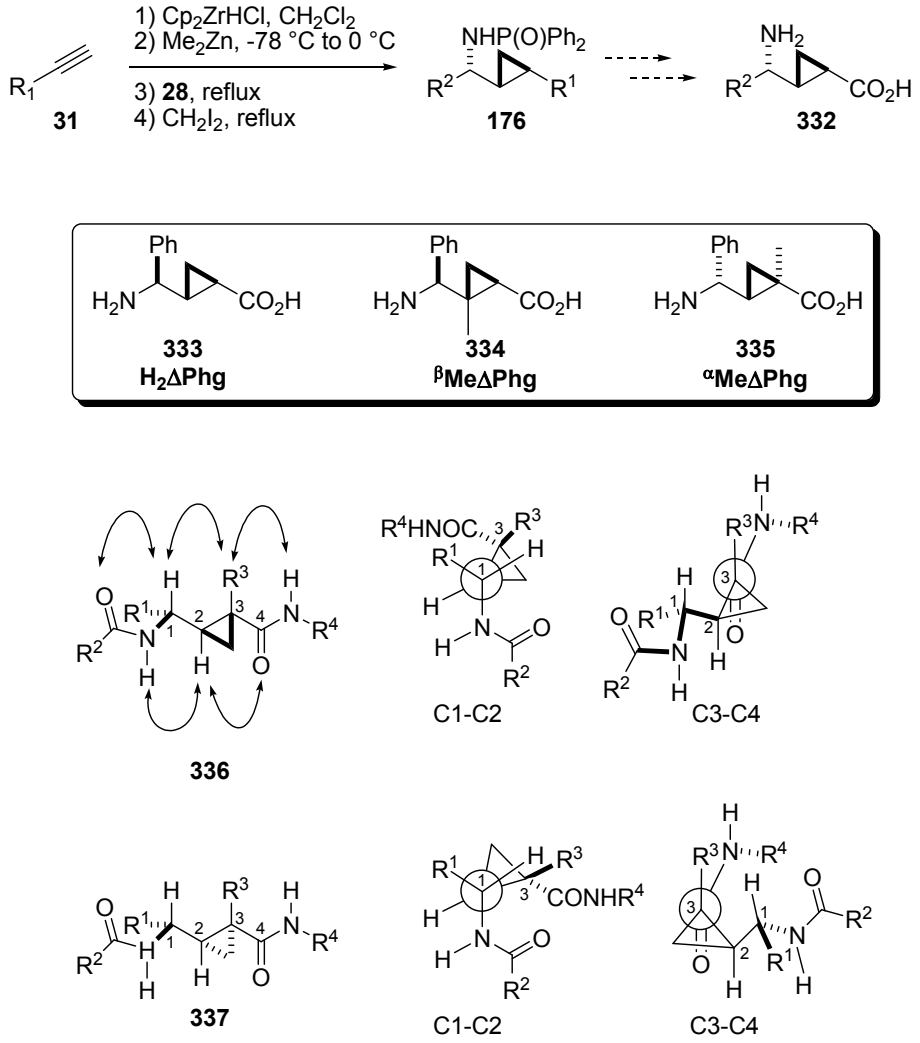


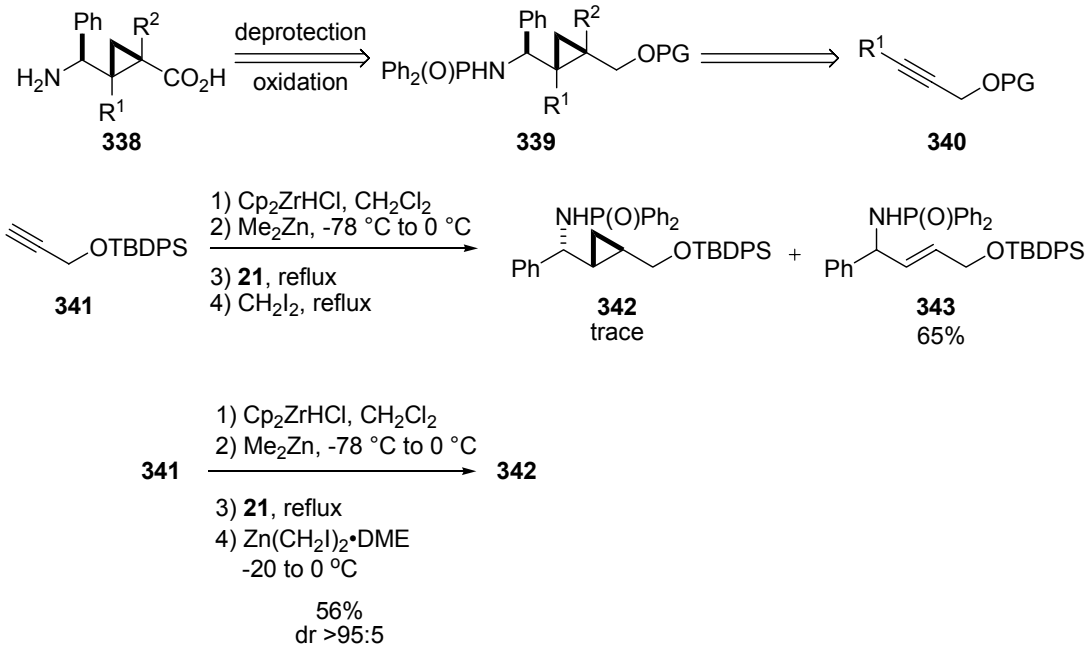
Figure 2.5. Proposed Cyclopropyl Amino Acids

2.2.1 Synthesis of Cyclopropyl Amino Acids

Our first-generation approach to ΔPhg involved the use of TBDPS-protected propargyl ether **341** in the Zr→Zn three-component condensation reaction (Scheme 2.5). Hydrozirconation of **341** followed by transmetalation to dimethylzinc, followed by the addition to imine **21** in CH_2Cl_2 at reflux was significantly slower than observed for the alkynes used thus far, however, a

[258] For the synthesis of γ-unsubstituted-α-,β-cyclopropyl-γ-amino acids, see Baxendale, I. R.; Ernst, M.; Krahnert, W.-R.; Ley, S. V. *Synlett* **2002**, 1641.

single product (presumably the allylic amide) was observed by TLC. Unfortunately, upon treatment with CH_2I_2, the desired amino cyclopropane **342** was not formed[259] and allylic amide **343** was isolated in good yield. It was believed that the σ-electron withdrawing character of the allylic ether sufficiently deactivated the alkene towards cyclopropanation under these conditions. While we had since moved on to another approach to this problem, the in situ cyclopropanation issue for propargyl ethers has also been rectified. Under otherwise identical conditions, the intermediate allylic phosphinamide was treated with $Zn(CH_2I)_2$[74] at 0 °C for 4 h, and the desired cyclopropane **342** was isolated as a single diastereomer in good yield. One could argue that the most direct route to the desired amino acid would be using a protected propynoic acid derivative (ie, an ABO or OBO ester); however since one oxygen sufficiently deactivated the alkyne towards cyclopropanation, we believed that the addition of more oxygenation at the propargylic carbon would further hinder the process.

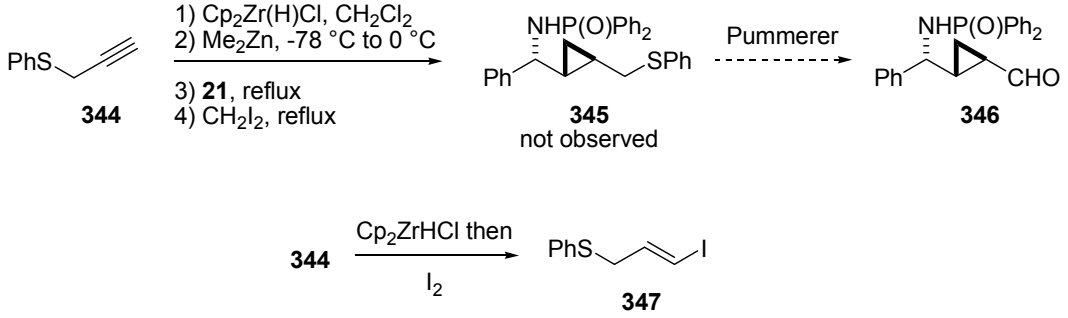


Scheme 2.5. First generation approach to cyclopropyl amino acids from propargyl ethers

A related idea for the preparation of an amino cyclopropane which was amenable to further functionalization to an amino acid relied on the propargyl sulfide **344** (Scheme 2.6). The sulfide could be converted to an aldehyde using the Pummerer rearrangement. However,

[259] Only traces of amino cyclopropane **342** were observed in the crude ^{1}H NMR.

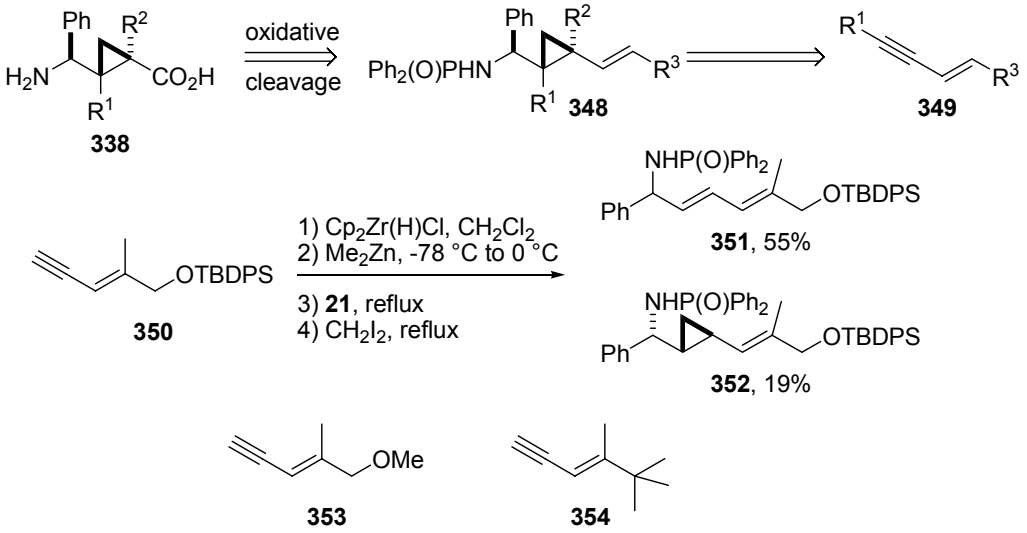
attempts to use this alkyne in the three-component formation of amino cyclopropanes failed, and upon work-up of the reaction there was a strong odor of thiophenol.[260] Hydrozironation of **344** and quenching with I_2 afforded the expected vinyl iodide suggesting that the addition of dimethylzinc was causing pre-mature decomposition of the reagent prior to imine addition.



Scheme 2.6. Attempted cyclopropane formation using propargyl phenyl sulfide

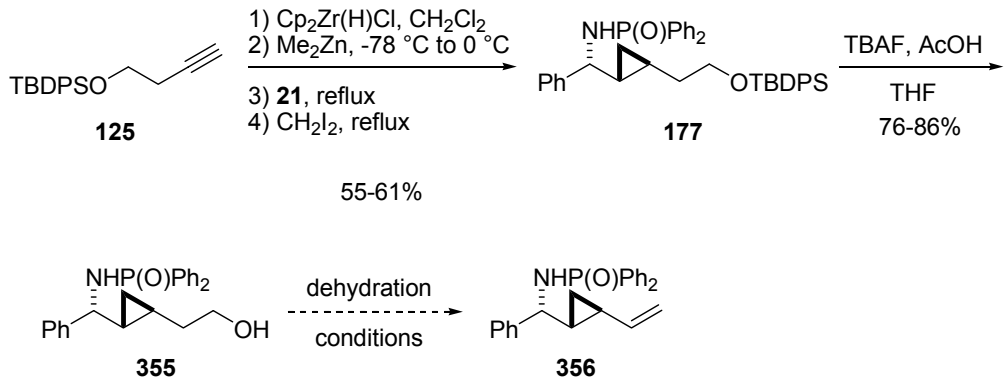
Our third approach hinged on the use of enynes as the nucleophilic component of the dimethylzinc-mediated cyclopropanation reaction (Scheme 2.7). As previously discussed (see Scheme 1.26, Chapter 1.3.1), enynes **143** and **195** did not afford the desired vinylcyclopropanes, instead giving exclusively biscyclopropanes **190** and **196** as single diastereomers.[261] Given our experience with the resistance of propargyl ethers to reaction under the cyclopropanation conditions, enyne **350** was prepared.[262] Unfortunately the deactivation extended to the allylic amide and the major product observed was dienyl amide **351** (55%) along with the desired vinylcyclopropane **352** (19%). Forcing this reaction by extending the reaction time (>72h) afforded greater quantities (ca. 35%) of **352**, however, this material was not easily separated from diene **351** and the corresponding biscyclopropane (not shown). Enynes **353** and **354** were also prepared and evaluated in this reaction, however mixtures of mono- and biscyclopropane, along with diene were observed.

[260] Imine was still present when the reaction was quenched, but not quantified due to its facile hydrolysis.
[261] As observed by crude ^{1}H NMR.
[262] Enyne's **350**, **353** and **354** were prepared in an analogous fashion to **143** and **195** (See Scheme 1.25).



Scheme 2.7. Second generation approach employing enynes

After preparation of amino cyclopropane **177**, we sought to take advantage of the functional groups present and transform the primary alcohol into an olefin by dehydration (Scheme 2.8). On modest scale (ca. 1.0 g of **21**), the desired amino cyclopropane **177** could be prepared in good yield (76%). On preparative scale (ca. 3.5 g imine), a marginal decrease in isolated yield (55-61%) was observed, however the overall throughput[263] was sufficient for our studies. Desilylation (TBAF, AcOH) afforded the requisite alcohol **355** for dehydration studies of the formation of vinyl cyclopropane **356**.



Scheme 2.8. Preparation of alcohol **355**

[263] Two 3.5 g scale reactions were run in parallel affording 8 g of **177** after combined work-up and purification.

The dehydration of alcohol **355** was anticipated to proceed without significant difficulty; in practice, this transformation was more challenging than expected (Table 2.1). Activation of the primary alcohol for elimination using a number of reagent combinations failed to afford the desired vinylcyclopropane in acceptable yield. Sulfonates (entries 1-3) were consistently poor and afforded, under optimal conditions (entry 2), only 20% of **356**. Conversion to the primary iodide (Ph_3P, I_2, imidazole) followed by elimination with DBU (entry 4) afforded only 35% of **356**. Furukawa's reagent,[264] DCC/CuCl,[265] and Ph_3P/DEAD (entries 5-8) failed to produce any detectable amounts of **356**, while an attempted Chugaev elimination[266] resulted in decomposition (Entry 9).

Table 2.1. Attempted dehydration of alcohol **355** to form vinylcyclopropane **356**

entry	dehydration conditions	yield of **356** (%)[a]
1	1) MsCl, Et_3N, THF, 0 °C 2) DBU, DMF, r.t to 120 °C	no desired product
2	1) MsCl, TEA, THF, 0 °C 2) K-O*t*-Bu, 18-crown-6, r.t	20%
3	1) Tf_2O, Et_3N, CH_2Cl_2, -78 °C 2) Warm to 0 °C	decomposition
4	1) Ph_3P, I_2, Imidazole, CH_3CN/Et_2O 2) DBU, DMF	35%
5	Furukawa's reagent (MsCl, DMAP, H_2O)[267]	no desired product
6	Furukawa's reagent, reflux	decomposition
7	DCC, CuCl, PhH, reflux[265]	no desired product
8	DEAD, Ph_3P, toluene, 90 °C	no desired product
9	1) NaH, CS_2 2) MeI 3) Xylenes, reflux[266]	decomposition

[a]Yield of isolated, analytically pure product based on alcohol **355**.

[264] (a) Furukawa, J.; Morisaki, N.; Kobayashi, H.; Iwasaki, S.; Nozoe, S.; Okuda, S. *Chem. Pharm. Bull.* **1985**, *33*, 440. (b) Comins, D. L.; Hong, H.; Salvador, J. M. *J. Org. Chem.* **1991**, *56*, 7197.

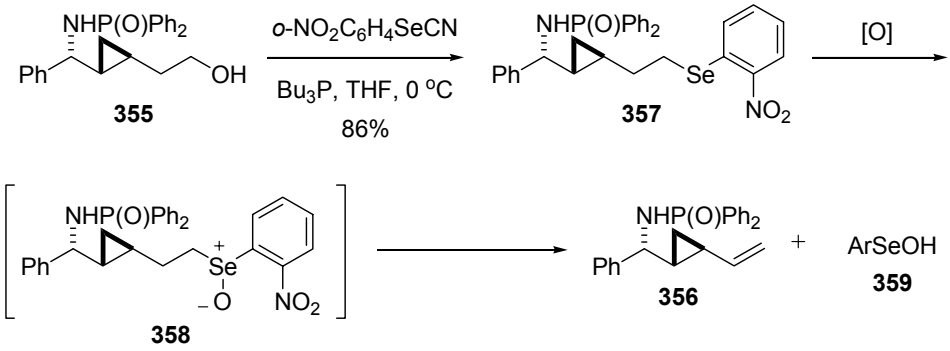
[265] (a) Alexandre, C.; Rouessac, F. *Bull. Soc. Chim. Fr.* **1971**, 1837. (b) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776.

[266] Bordwell, F. G.; Landis, P. S. *J. Am. Chem. Soc.* **1959**, *81*, 228.

[267] Furukawa's reagent was prepared by addition of H_2O (0.29 mL) to a solution of DMAP (2.4 g) in dry CH_2Cl_2 (52 mL). The mixture was treated with MsCl (3.1 mL) and stirred until all solid was dissolved (~2 days).

We turned our attention to the conditions developed by Grieco[268] for the dehydration of alcohols (Table 2.2). The intermediate selenide **357** was prepared in excellent yield (80-88%) with little variation, however there was significant deviation (0-57%) in the isolated yield of vinylcyclopropane **356** (entries 1-4). After searching the literature for the reactivity of selenium and selenoxides, we were delighted to discover that the low temperature oxidation of the selenide **357** followed by treatment with *i*-Pr_2NH and warming to r.t. reproducibly afforded **356** in excellent isolated yield (88%) (entry 5). In fact, the reaction could be carried out without chromatographic purification of **357** and the crude selenide was dissolved in dry CH_2Cl_2 and treated at -40 °C with buffered *m*-CPBA.

Table 2.2. Optimization of the oxidation-elimination of selenide **357**



entry	oxidation protocol	yield of **356** (%)
1	H_2O_2, THF	25-43% [a]
2	$NaIO_4$, THF/H_2O	57% [a]
3	Bu_4NIO_4, THF/H_2O	no desired product
4	*m*-CPBA, CH_2Cl_2, 0 °C to r.t	35% [a]
5	1) *m*-CPBA, Na_2HPO_4, CH_2Cl_2, -40 °C 2) *i*-Pr_2NH, -40 °C to r.t	88%

[a]Yield of isolated, analytically pure product based upon selenide **357**

Upon consumption of **357**,[269] *i*-Pr_2NH was added and the reaction mixture was warmed to r.t. and the elimination proceeded to afford **356** (86%, 2 steps).[270] The presumed failure of the selenoxide elimination was due to the presence of the by-product of elimination, arylselenenic

[268] (a) Grieco, P. A.; Miyashita, M. *J. Org. Chem.* **1974**, *39*, 120. (b) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.
[269] The formation of **357** was not observed at -40 °C.
[270] (a) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434. (b) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697.

acid **359**. Reich and others have shown that arylselenenic acids disproportionate into arylseleninic acids and diaryldiselenides (Figure 2.6). Fortunately, **359** can be trapped with a secondary amine (ie, *i*-Pr_2NH) forming the stable diisopropyl-selenenamide **362**, retarding possible electrophilic decomposition[271,272] pathways for vinylcyclo-propane **356**.

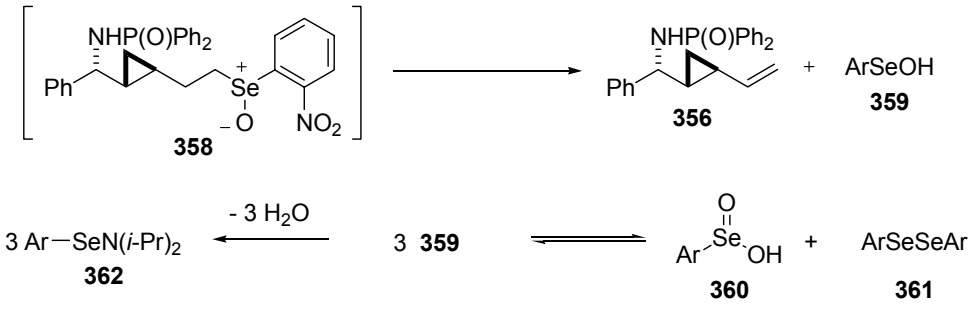
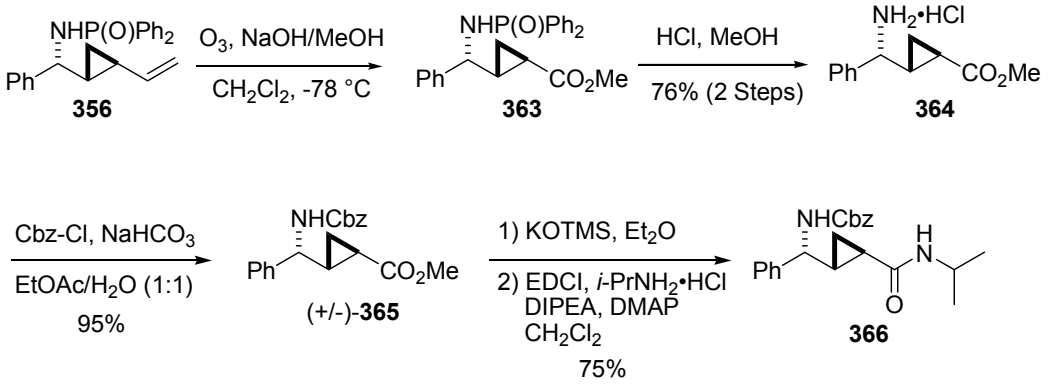


Figure 2.6. Trapping of the byproduct of selenoxide elimination

After the efficient preparation of **356**, the synthesis of our ΔPhg derivative continued with the oxidative cleavage of the terminal olefin (Scheme 2.9). According to the ozonlysis protocol developed by Marshall,[52] a solution of **356** in basic methanol (4:1, CH_2Cl_2/2.5 M NaOH in MeOH) was ozonized at -78 °C affording the fully protected amino acid ester **363**. Crude **363** was treated with a solution of HCl in MeOH to remove the phosphinoyl protective group, and when the deprotection was judged to be complete by TLC analysis, the MeOH solution was poured into dry Et_2O and the pure hydrochloride salt **364** was isolated by filtration (76%, 2 steps). The amino function was re-protected under bi-phasic conditions (Cbz-Cl, $NaHCO_3$) to afford racemic Cbz-H_2ΔPhg-OMe. Saponification (KOTMS/Et_2O)[273] and coupling with *i*-$PrNH_2$•HCl (EDCI/DMAP/DIPEA) afforded the isopropylamide derivative **366**. We were able to obtain crystals suitable for x-ray diffraction by the slow evaporation of a solution of **366** in a mixture of CH_2Cl_2 and toluene affording long stacks of molecules arranged in a parallel assembly. The general structure observed is extended as desired; however there is a considerable

[271] **359** and **361** are electrophilic sources of selenium while **360** is acidic (pK_a ~3.8)[272]
[272] The pK_a of *o*-$NO_2C_6H_4SeOH$ has been measured to be 10.45 (ref. 272b) while $PhSeO_2H$ has a measured pK_a of 4.79 (ref. 272a). The pKa of PhSeOH has been approximated to be ~11.5 (ref. 272b). On the basis of this approximation, the pK_a of *o*-$NO_2C_6H_4SeO_2H$ can be estimated to be ~3.8. *Cf.* (a) McCullogh, J. D.; Gould, E. S. *J. Am. Chem. Soc.* **1949**, *71*, 674. (b) Kang, S.-I.; Kice, J. L. *J. Org. Chem.* **1986**, *51*, 287.
[273] Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831.

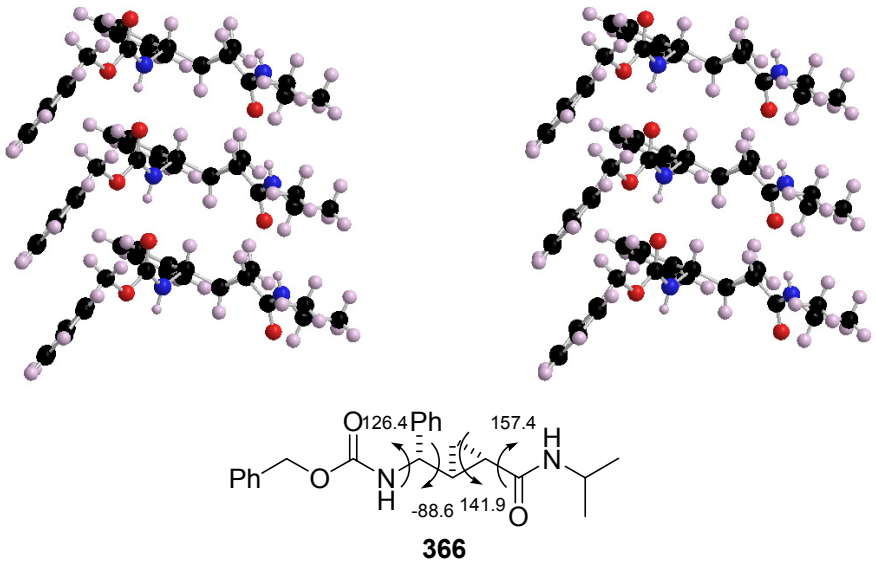
turn initiated about the N-C4-C3-C2 dihedral angle (-88.6°). The remaining dihedral angles are within the range of angles observed in extended peptides (ie, β-sheets). As part of our continuing evaluation of our allylic- and *C*-cyclopropylalkylamides in various biological screens,[274] phosphinamide **363** was found to inhibit pre-mRNA splicing of CD45 (~5 μM) with a novel mechanism of action. A focused library of analogues will be prepared in the UPCMLD with the aim increasing the potency and develop a biological probe with hopes of determining the molecular target.[275]



Scheme 2.9. Synthesis of Cbz-H_2ΔPhg-NH^{i}Pr, **366**

[274] A library of allylic and *C*-cyclopropylalkylamides prepared during the development of the methodologies described in Chapter 1 was evaluated for anti-estrogenic activity in collaboration with Professor Billy Day. An interesting lead structure prepared by Dr. Chris Kendall was discovered amongst the compounds. A preliminary communication detailing these efforts has recently been published. Janjic, J. M.; Mu, Y.; Kendall, C.; Stephenson, C. R. J.; Balachandran, B.; Raccor, B. S.; Lu, Y.; Zhu, G.; Xie, W.; Wipf, P.; Day, B. W. *Biorg. Med. Chem.* **2005**, *13*, 157.

[275] This work has been carried out in collaboration with Prof. Kristen Lynch at the University of Texas, Southwestern Medical Center at Dallas.



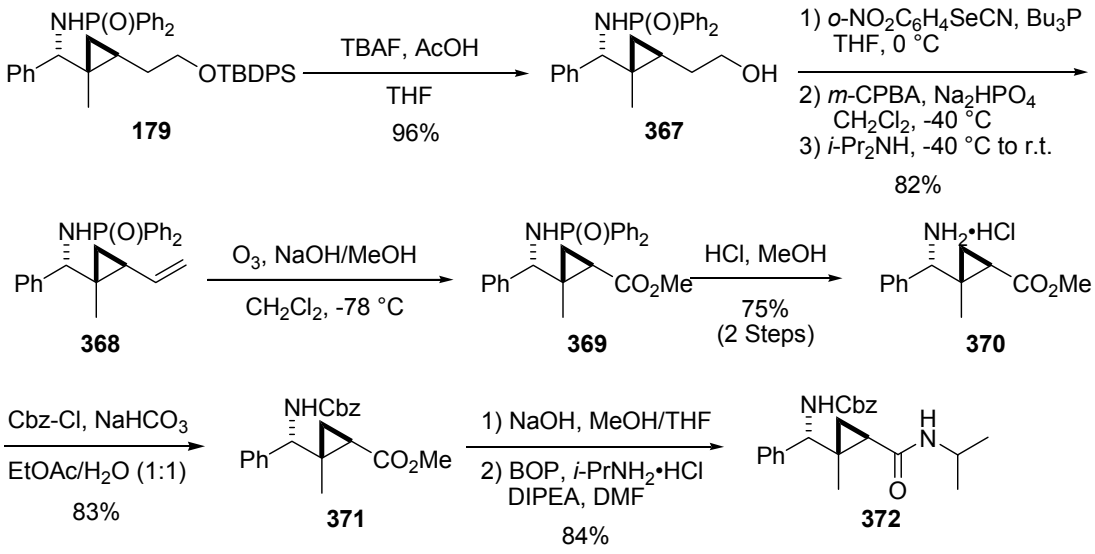
366

Figure 2.7. Stereoview of the Chem3D representation of the x-ray crystal structure of **366** and representative dihedral angles[276]

The β-methyl-substituted-γ-amino acid derivative **371** was prepared in an analogous fashion to **178** beginning with the previously described *C*-cyclopropylalkylamide **178** (Scheme 2.10). Desilylation (TBAF, AcOH) afforded alcohol **367** in excellent yield. Under the optimized Grieco elimination conditions,[268] vinylcyclopropane **368** was prepared in very good yield. Oxidative cleavage[52] of the olefin afforded ester **369** which was dephosphinoylated without purification to afford the hydrochloride salt **370** (75%, two steps). *N*-Protection as a benzyl carbamate followed by saponification (NaOH/MeOH/THF) and BOP coupling with *i*-$PrNH_2$•HCl afforded the amide derivative Cbz-$^{\beta}$MeΔPhg-NH^{i}Pr. A sheet-like structure is once again found in the crystal structure of **372**,[277] however, the arrangement is anti-parallel and the β-methyl substituent appears to preclude the formation of higher order sheets. A more pronounced

[276] See Appendix B for crystal coordinates.
[277] Crystals suitable for x-ray diffraction studies were obtained from slow evaporation of a solution of **372** in CH_2Cl_2 and toluene (ca. 3 drops).

turn is initiated about the N-C4-C3-C2 dihedral angle (-77.6°) such that the compound nearly folds onto itself forming a β-turn motif.[278]



Scheme 2.10. Synthesis of Cbz-$^{\beta}$MeΔPhg-NH^{i}Pr, **372**

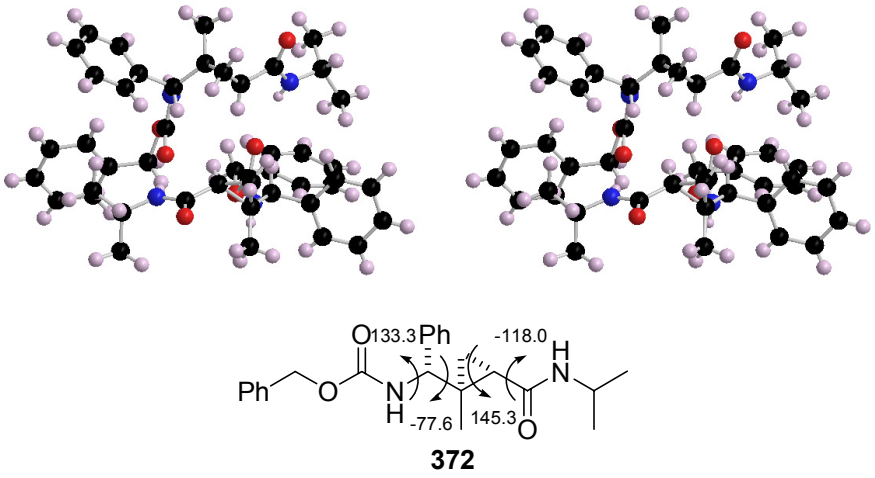


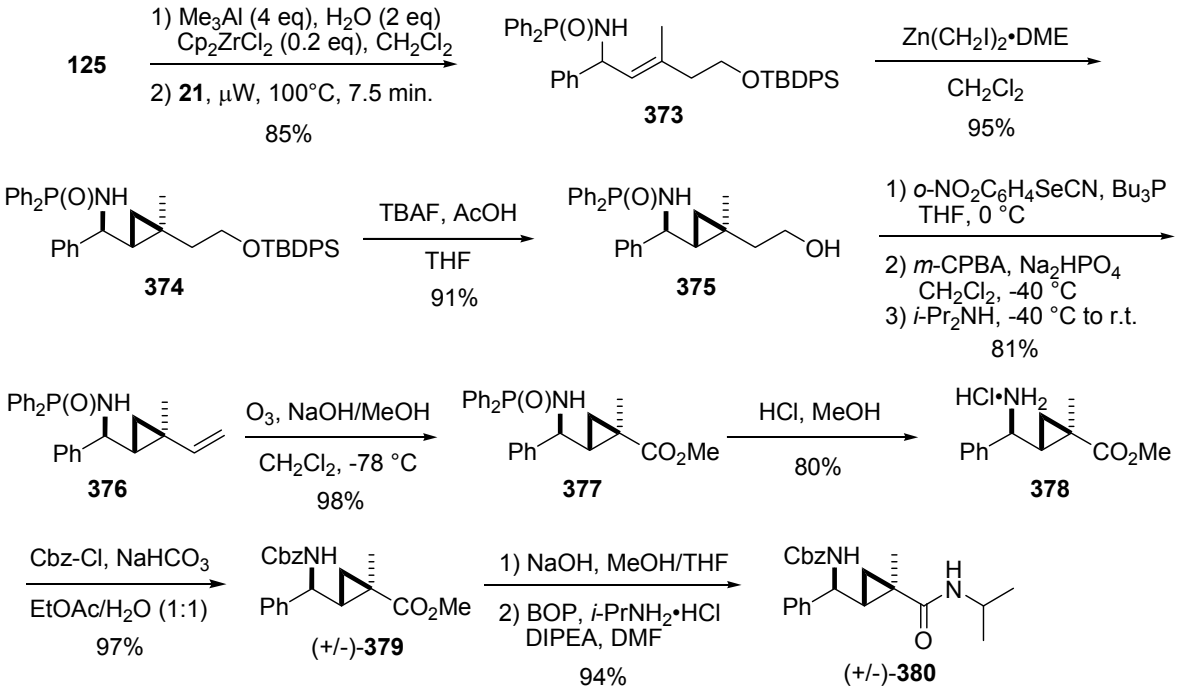
Figure 2.8. Stereoview of the Chem3D representation of the x-ray crystal structure of **372** and representative dihedral angles[279]

[278] Indeed, peptide mimetics with an extra carbon atom in the backbone sequence have been prepared by Mr. Jingbo Xiao and β-turn motifs have been observed. For example, see Wipf, P.; Xiao, J. *Org. Lett*. **2005**, *7*, 103.
[279] See Appendix C for crystal coordinates.

The final cyclopropyl amino acid derivative that we wanted to prepare bears a methyl substituent in the α-position and required the use of the tandem water-accelerated methyl alumination-imine addition reaction developed in the Wipf group in 2002.[168,280] It has been demonstrated that the vinylalanes generated under these conditions could be added to *N*-diphenylphosphinoyl imines,[281] although the reaction was slow (ca. 24-48 h for complete conversion) even at r.t. Given our success with the application of microwave technology to the vinylzinc additions to imines, we attempted the addition of the vinylalane derived from **125** to imine **21** in the microwave. Indeed, the addition proceeds smoothly at 100 °C in only 7.5 minutes, however reaction throughput was limited to ~0.25 g of **21** per reaction (Scheme 2.11). Fortunately this issue was resolved using the automated Personal Chemistry microwave reactor. Alkyne **125** was treated under water-accelerated carboalumination conditions on preparative scale and added in equal portions to sixteen microwave tubes containing 0.25 g of **21**. The automated reactor heated each vessel at 100 °C for the required time and, upon completion of the sequence (~2.5 h), the reactions were combined for work-up and purification affording **373** in excellent yield (85%). Simmons-Smith cyclopropanation[74] using the DME complex of $Zn(CH_2I)_2$[282] gave amino cyclopropane **374** (95%, dr >95:5). Not surprisingly, the stereochemical outcome of this cyclopropanation reaction was in favor of the *syn*-diastereomer while the *anti*-diastereomer was favored using the Zr→Zn methodology (see Figure 1.7, Chapter 1.3.1). Desilylation (TBAF/AcOH, 91%) followed by Grieco elimination[268] afforded **376** (81%). Ozonolysis in basic methanol[52] followed by removal of the diphenylphosphinoyl protective group gave hydrochloride salt **378** (78%, two steps). Protection of the amino functionality as the benzyl carbamate ($NaHCO_3$, Cbz-Cl) followed by saponification (NaOH/MeOH/THF) and BOP coupling afforded racemic Cbz-$^{\alpha}$MeΔPhg-NH^{i}Pr (97%). The structural arrangement in the solid state of **380** is similar to that observed for **372**, the α-methyl-substituted *i*-Pr amide derivative (+/-)-**380** crystallized as a dimer, also in an anti-parallel array. However, the dihedral angles are all >125° and the overall structural is nearly fully extended via three-fold minimization of $A^{1,3}$-strain across the carbamate, the cyclopropane and the amide bond. Interestingly, the methyl

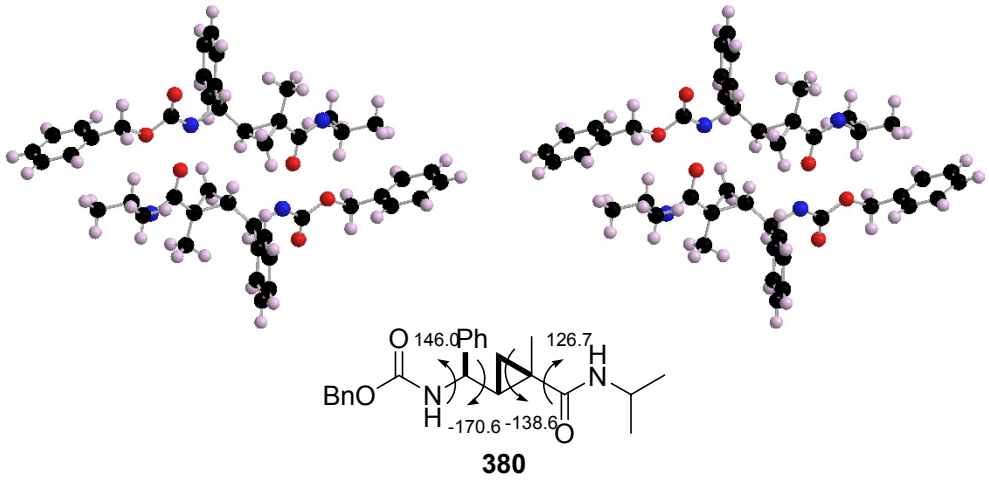
[280] Wipf, P.; Nunes, R. L.; Ribe, S. *Helv. Chim. Acta* **2002**, *85*, 3478.
[281] Ribe, S. D. Ph.D Dissertation, University of Pittsburgh, 2003.
[282] $Zn(CH_2I)_2$ has been reported as an explosion hazard and the DME complex is suggested as a safe alternative for reactions run using ≥1 mmol of reagent. For the original report, see Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081.

group once again prohibits higher order sheet formation, limiting aggregation to dimers. We were very excited about the potential of oligopeptides based on this scaffold to adopt an extended conformation. The racemic amide **380** was found to be an agonist of the Pregnane X receptor (PXR), a xenobiotic nuclear receptor which regulates the expression of many genes responsible for drug metabolism.[283] The optically pure amides (-)-**380** and (+)-**380** were also prepared for biological evaluation under analogous conditions beginning with optically pure tartrate salts **385** or **386** (vide infra). An interesting species-dependent stereoselectivity was observed for the enantiomeric amides; (+)-**380** was more active for hPXR, whereas (-)-**380** exhibited increased activity for mPXR.



Scheme 2.11. Microwave-assisted synthesis of Cbz-$^{\alpha}$MeΔPhg-NH^{i}Pr ((+/-)-**380**)

[283] Mu, Y.; Stephenson, C. R. J.; Kendall, C.; Saini, S. P. S.; Toma, D.; Ren, S.; Cai, H.; Strom, S. C.; Day, B. W.; Wipf, P.; Xie, W. *Submitted to Mol. Pharm.*



380

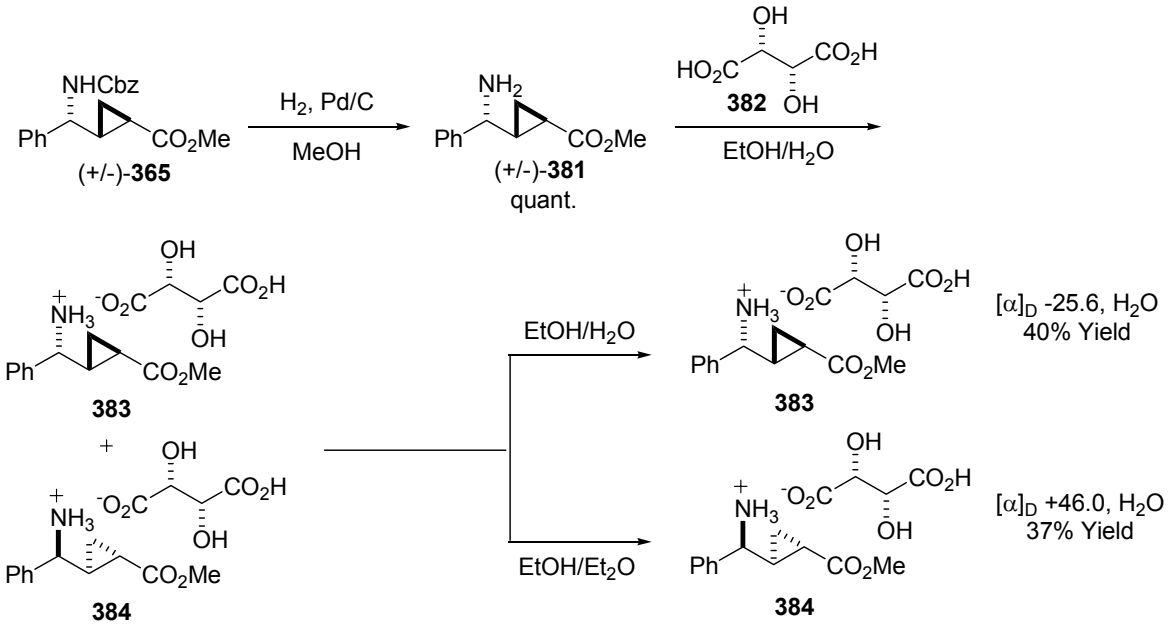
Figure 2.9. Stereoview of the Chem3D representation of the x-ray crystal structure of (+/-)-**380** and representative dihedral angles[284]

2.2.2 Resolution of the Racemates and Determination of Absolute Configuration

In order to prepare oligomers of α,β-cyclopropyl-γ-amino acids and examine their conformational preferences, we required access to optically pure building blocks. Unfortunately, we are currently unable to add alkenylzirconocenes to imines to afford optically enriched allylic- or *C*-cyclopropylalkylamides.[285] A classical resolution by fractional crystallization seemed to be the most straightforward solution to this problem (Scheme 2.12).[286] On the basis of the crystal structures of simple amide derivatives that we had obtained, we chose to resolve only amino esters **365** and **379** since they appeared to possess the attributes that we desired in our building blocks. That is, they seemed to favor formation of organized secondary structures in the crystalline states. Accordingly, hydrogenolysis of (+/-)-**365** and heating the resultant amino cyclopropane in EtOH/H_2O with *L*-tartaric acid followed by concentration to dryness afforded a diastereomeric mixture of tartrate salts **383** and **384**. Fractional crystallization from EtOH/H_2O afforded predominantly **383** which was re-crystallized until the optical rotation was constant

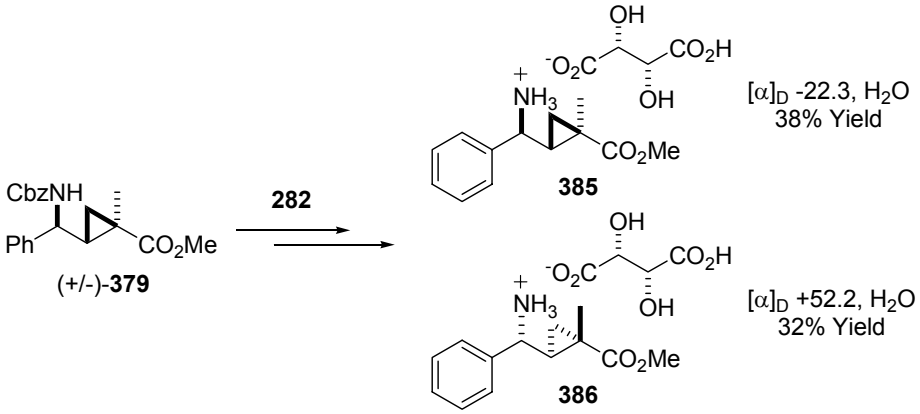
[284] See Appendix D for crystal coordinates.
[285] For a stimulating discussion of the attempted solutions to this problem, see Kendall, C., Ph.D Dissertation, University of Pittsburgh, 2004.
[286] Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*, Wiley, New York, 1981.

(40%, $[\alpha]_D$ -25.6, *c* 0.57 H_2O). The mother liquor from the first crystallization contained mostly **384**, which was highly soluble in EtOH. Re-crystallization of **384** from EtOH/Et_2O (2x) afforded **384** (37%, $[\alpha]_D$ +46.0, *c* 0.51 H_2O) as a colorless solid.[287]



Scheme 2.12. Resolution of (+/-)-**381**

The resolution of (+/-)-**379** was carried out under otherwise identical conditions as shown in Scheme 2.12 beginning with Cbz deprotection and tartrate salt formation (Scheme 2.13).[288]

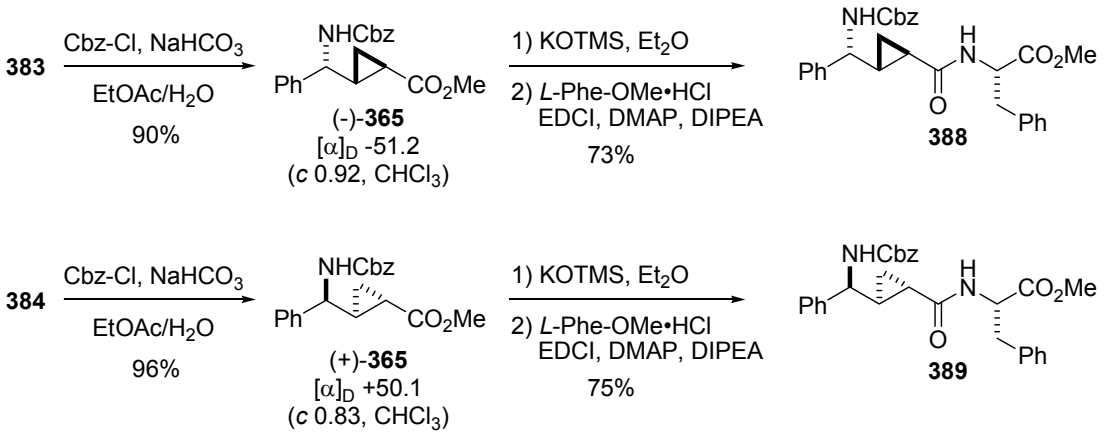


Scheme 2.13. Resolution of (+/-)-**379**

[287] The resolution was not optimized, and it is expected optimization of the acid could improve the recovery.
[288] See experimental section for details.

After the tartrate salts were resolved, the only information concerning the stereochemistry of the amino acids was their optical rotations. In order to ascertain the absolute stereochemistry of **383** and **384**, a number of derivatives were prepared for analysis by x-ray diffraction (Scheme 2.15).[289] The tartrate salts were easily *N*-protected to give **(-)-365** and **(+)-365** in excellent yields. Saponification with KOTMS in Et_2O followed by EDCI coupling with *L*-Phe-OMe•HCl afforded the dipeptides **388** and **389** in good yields (73 and 75%, respectively). Unfortunately, these dipeptides did not afford crystals suitable for x-ray diffraction studies, but they were useful for the HPLC determination of enantiomeric purity. The crude coupling reactions of *L*-phenylalanine with (+)-**365** and (-)-**365** were analyzed by HPLC and compared with the mixture of diastereomers prepared by coupling with (+/-)-**365**.[290] In the analysis of the reaction of (-)-**365**, the minor diastereomer was not detected by HPLC ((-)-**356** *de* >99%) while the ratio for the corresponding coupling of (+)-**365** was 99.3:0.7 (*de* 98.6%).

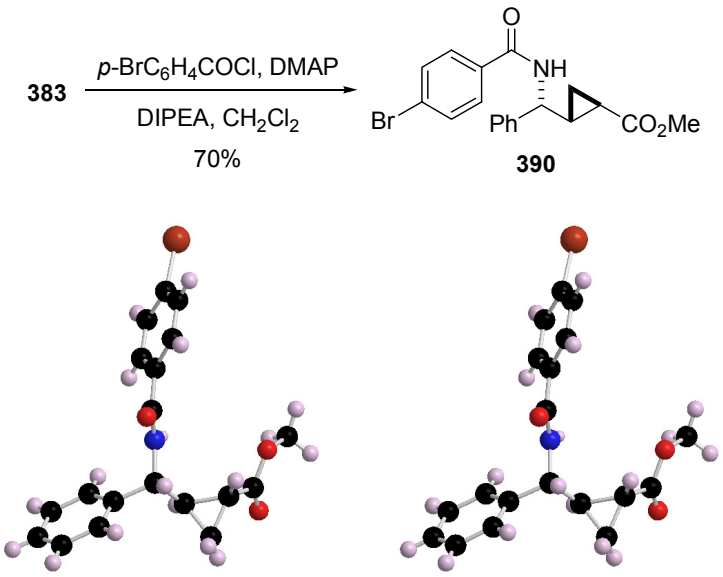
We were happy to find that the *p*-bromobenzamide derivative **390** could be prepared directly from **383** (*p*-BrC_6H_4COCl, DMAP, 70%) to afford a colorless crystalline solid. Crystals suitable for single crystal x-ray diffraction analysis were obtained from a mixture of CH_2Cl_2 and toluene, confirming the absolute configuration[291] of **390** (Scheme 2.15). Although the configuration at the nitrogen-bearing stereocenter is *R*, it has the same sense of chirality (*L*) as the corresponding natural α-amino acids.



Scheme 2.14. Preparation of phenylalanine derivatives **388** and **389** for HPLC analysis

[289] Attempts to obtain crystals suitable for x-ray diffraction analysis from **383**, **384**, **385** and **386** were unsuccessful.
[290] HPLC conditions: Microsorb-MV 100 column, 3:1 hexanes/EtOAc, **388** 13.2 min; **389** 10.8 min.
[291] For the use of x-ray for the determination of absolute stereochemistry using heavy atoms, see Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876.

A similar analysis was carried out on the tartrate salts **385** and **386**. Benzyl carbamate formation (Cbz-Cl, $NaHCO_3$) afforded (-)-**379** and (+)-**379** in excellent yields (Scheme 2.16). In this case, the coupling reaction of (-)-**379** with *L*-Phe-OMe•HCl afforded only modest yield of **391** (59%). Saponification of (+)-**379** with 2N NaOH solution in MeOH/THF followed by BOP coupling afforded **392** as a colorless solid in very good yield (85%). The NaOH conditions are the best developed thus far and would be the method of choice for future coupling reactions since fewer side products are observed during the saponification compared with the KOTMS reaction.[292] The diastereomeric purity of **391** and **392** was established using HPLC analysis of the crude coupling reactions (**391** and **392**, de >99%).[293]

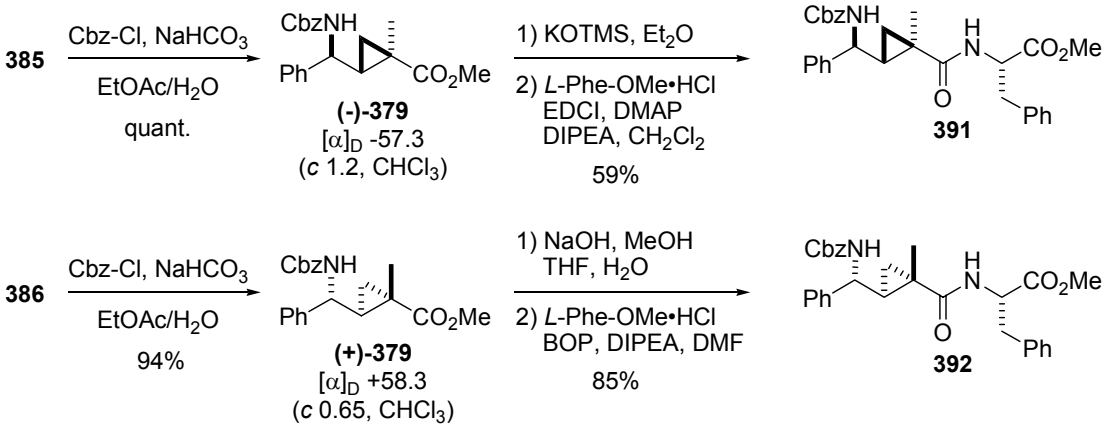


Scheme 2.15. Synthesis of derivative **390** for determination of absolute configuration[294]

The absolute configuration of the $^{\alpha}$MeΔPhg scaffold was determined by x-ray crystallographic analysis of **391** (Figure 2.10).[295] In terms of the solid state structure of our peptide mimics, this compound also crystallized as a dimer in an anti-parallel arrangement. While this represents the largest linear peptide which we have been able to crystallize to date, the

[292] LiOH mediated saponifications are slow at r.t. and reagents which require warming above r.t. lead to the formation of unidentified side products.
[293] HPLC conditions: Microsorb-MV 100 column, 7:3 hexanes/EtOAc, **392** 4.5 min; **391** 5.9 min.
[294] See Appendix E for crystal coordinates.
[295] We were able to grow crystals suitable for x-ray diffraction analysis from a mixture of hexanes and ethyl acetate.

extension of the linear structure into the second amino acid is encouraging for future analysis of some of the larger oligopeptides which have been prepared (vide infra).



Scheme 2.16. Synthesis of derivatives of **391** and **392** for determination of absolute configuration and HPLC analysis

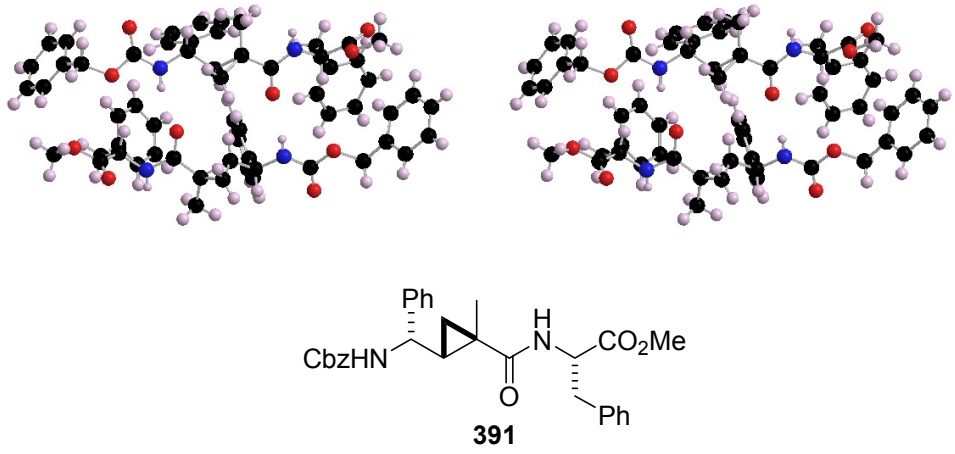


Figure 2.10. Stereoview of the Chem3D representation of the x-ray crystal structure of **391**[296]

[296] See Appendix F for crystal coordinates.

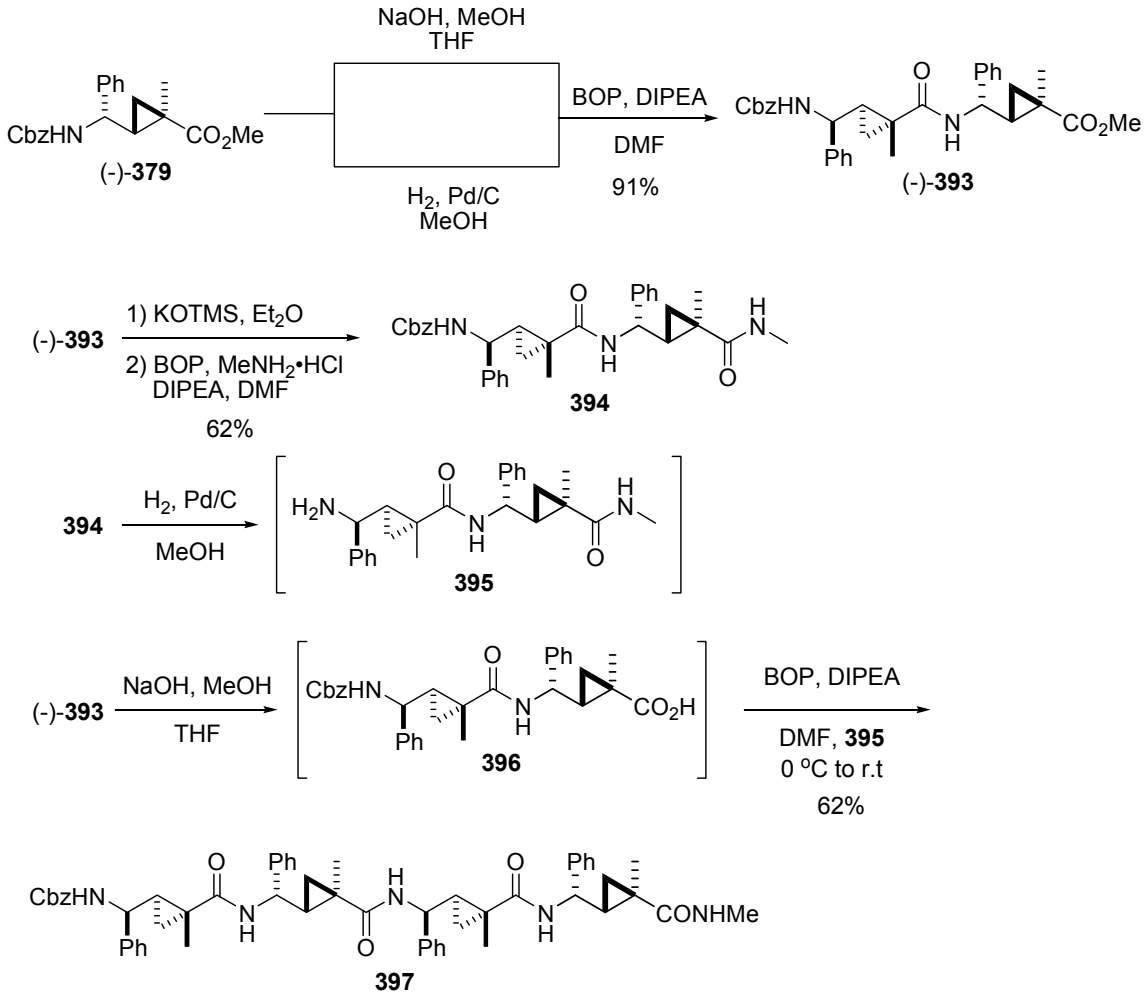
2.2.3 Synthesis of Cyclopropyl-γ-Amino Amide Oligomers

The structural data that we have amassed to date indicates that the $^{\alpha}$MeΔPhg scaffold is the most promising for stabilization of extended structures. It was our intention to prepare the dimer, tetramer and octamer of **335** for x-ray diffraction studies (Scheme 2.17). Saponification of (-)-**379** (NaOH/MeOH/THF) and coupling (BOP, DIPEA, DMF) with the free amine derived from Cbz-deprotection (H_2, Pd/C, MeOH) afforded the dipeptide (-)-**393** in excellent yield (91%). The dimer was divided into two portions for the preparation of tetramer **397**. Saponification (KOTMS, Et_2O) of (-)-**393** followed by coupling with $MeNH_2$•HCl (BOP, DIPEA, DMF) afforded the methyl amide **394** in modest yield (62%). The benzyl carbamate was removed (H_2, Pd/C, MeOH) to afford the intermediate amine **395**. Dipeptide (-)-**393** was saponified (2 N NaOH, MeOH, THF) and coupled to **395** (BOP, DIPEA, DMF) to give **397** in moderate yield (62%).

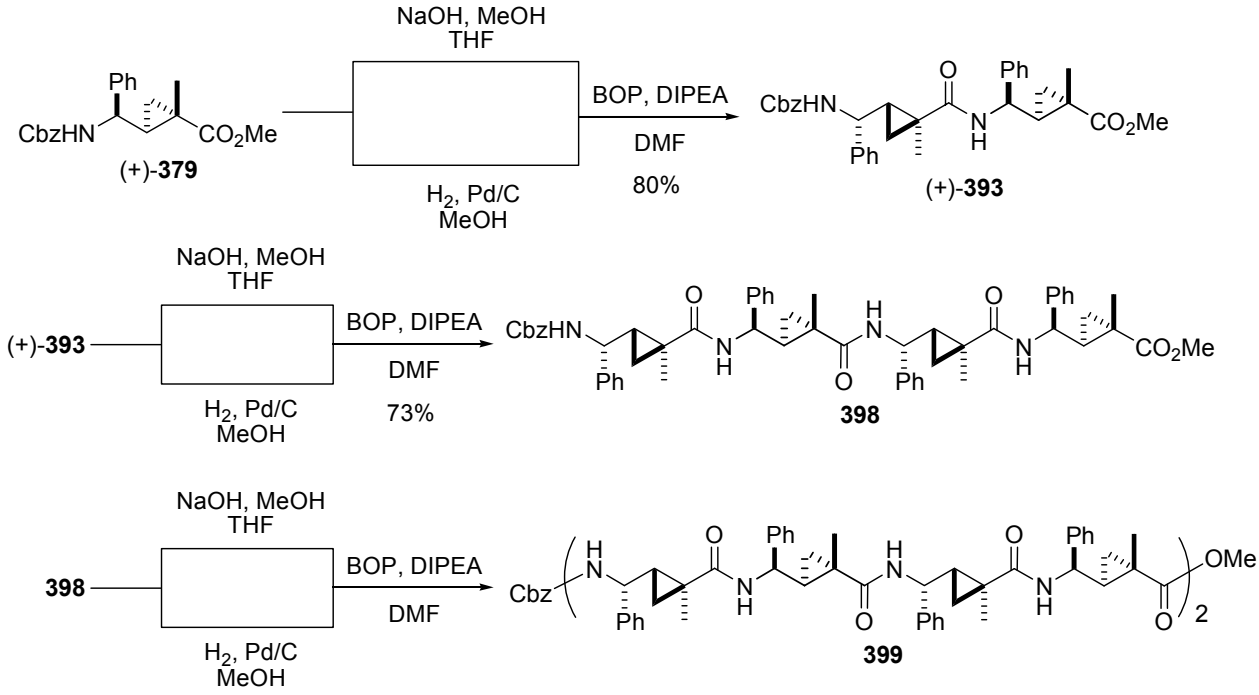
While preparing **397**, it quickly became apparent that there would not be enough material in this enantiomeric series to complete the synthesis of the desired octapeptide **399**. Thus, **399** was prepared in the antipodal series beginning with (+)-**379** (Scheme 2.18). Saponification (NaOH, MeOH, THF) and deprotection of the carbamate afforded the coupling partners for dimer preparation. The amine and the acid were coupled in DMF (BOP, DIPEA) to afford the dimer (+)-**379** (80%). In much the same fashion as shown in Scheme 2.17, tetrapeptide **398** was prepared in good yield (73%). At this stage, a small amount of **398** was kept for crystallization.

The majority of the material was split into two flasks for the preparation of the amine and acid coupling partners (NaOH, MeOH, THF or H_2, Pd/C, MeOH). BOP coupling afforded excellent mass recovery of the desired octapeptide. The crude material was shown to contain >90% of the desired peptide by ^{1}H NMR analysis in $CDCl_3$. However, upon concentration of this sample and solvent removal under high vacuum, the resultant colorless solid could not be dissolved in any solvent suitable for further purification.[297]

[297] Similarly, attempts to recrystallize this material were unsuccessful.



Scheme 2.17. Synthesis of di- and tetrapeptides **394** and **397** from (-)-**379**

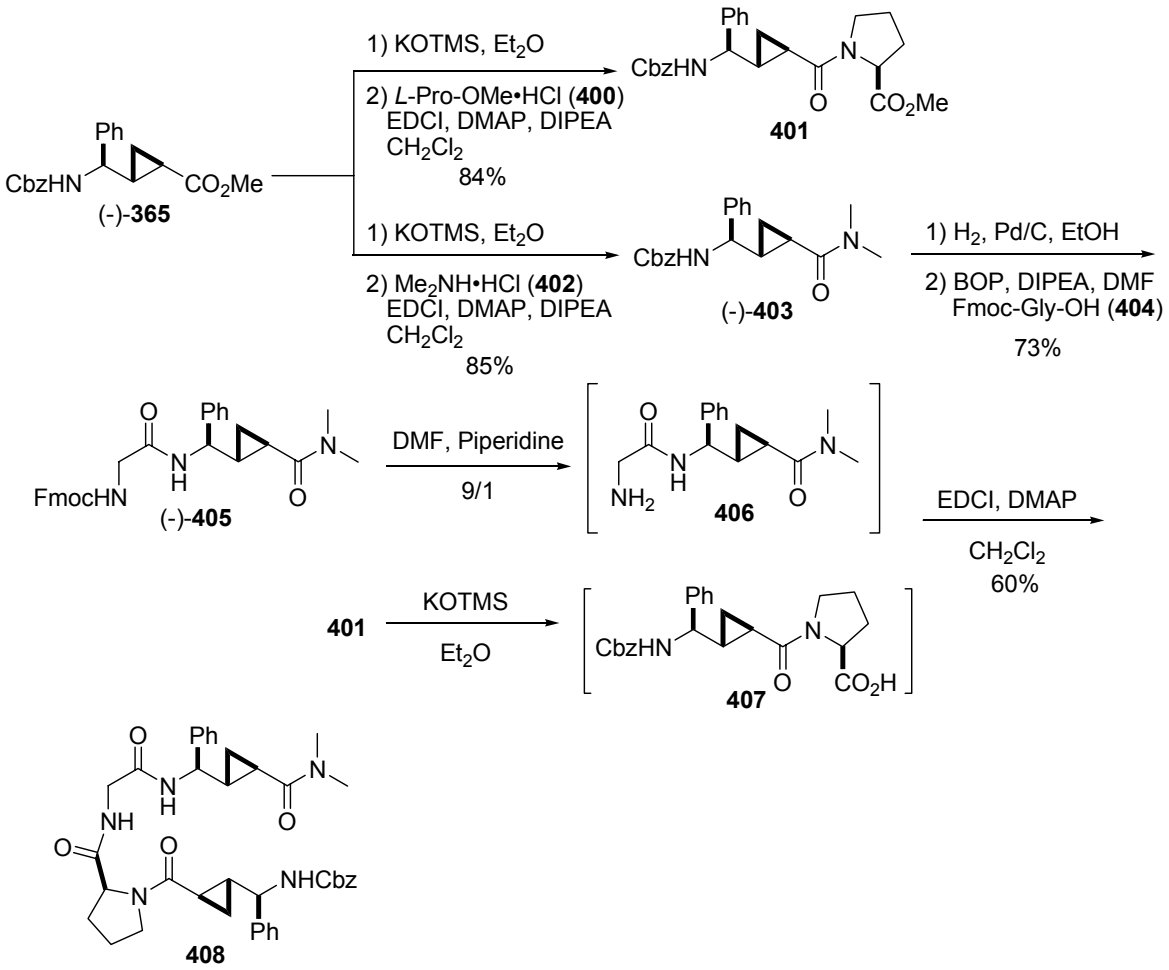


Scheme 2.18. Attempted synthesis of octamer **399**

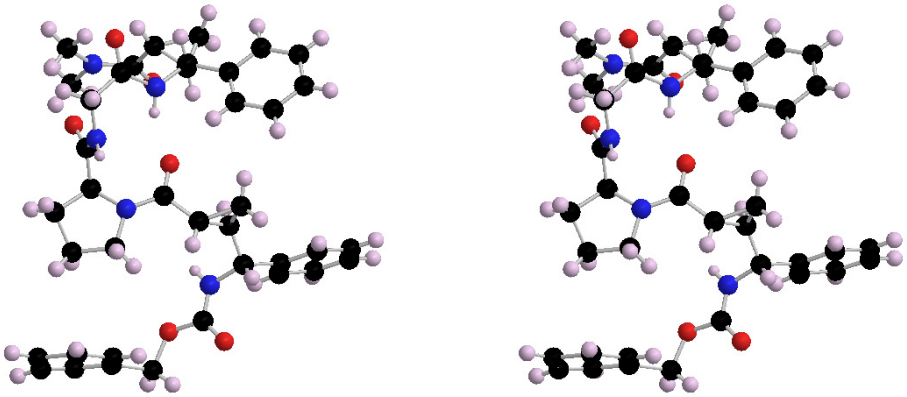
2.2.4 Synthesis of Minimal β-Hairpins

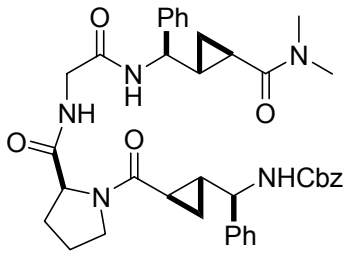
We were forced to rely heavily upon x-ray crystallography to study the linear peptides prepared in the previous section; however we were unable to secure a crystal structure for anything larger than a dipeptide. In order to establish the structural preferences of our cyclopropyl amino acid derivatives in solution, we decided to study their effects on stabilizing β-hairpin formation. The β-hairpin is a common structural motif found in peptides and proteins where two anti-parallel β-strands are connected by a two-amino acid loop known as a β-turn. Due to the structural similarities between our cyclopropyl amino acids and the vinylogous amino acids prepared by Schreiber and co-workers, we decided to use an *L*-Pro-Gly insert to induce β-turn formation. Rather than a linear synthesis of tetrapeptide **408**, we chose a convergent approach disconnecting into two fragment peptides at the Pro-Gly linkage (Scheme 2.19). Thus, beginning with Cbz-*L*-H_2ΔPhg-OMe, saponification (KOTMS, Et_2O) and coupling with either *L*-Pro-OMe•HCl, **400**, or Me_2NH•HCl (EDCI, DMAP, DIPEA) afforded the dipeptide **401** (84%) and the dimethylamide (-)-**403** (85%). Deprotection of the benzyl carbamate of (-)-**403** (H_2, Pd/C, MeOH) followed by coupling with Fmoc-Gly-OH, **404** (BOP, DIPEA) afforded dipeptide

(-)-**405** in good yield (73%). Fmoc deprotection (10% piperidine in DMF) of (-)-**405** and saponification of methyl ester **401** (KOTMS, Et_2O) afforded the coupling partners **406** and **407**. Fragment coupling (EDCI, DMAP) afforded the desired tetrapeptide **408** (60%) as a colorless solid. We were also able to secure the solid state structure of the supposed β-hairpin **408** as crystals were grown from a standing solution in DMSO. Interestingly, the β-turn structure that was built into the system (Pro-Gly) is preserved in the x-ray structure, however the lack of hydrogen bonding at the termini which would be necessary to extend the β-hairpin is obvious (vide infra). In fact, the amino acid residues are arranged such that intramolecular contact between residues is minimal.



Scheme 2.19. Synthesis of tetrapeptide **408**



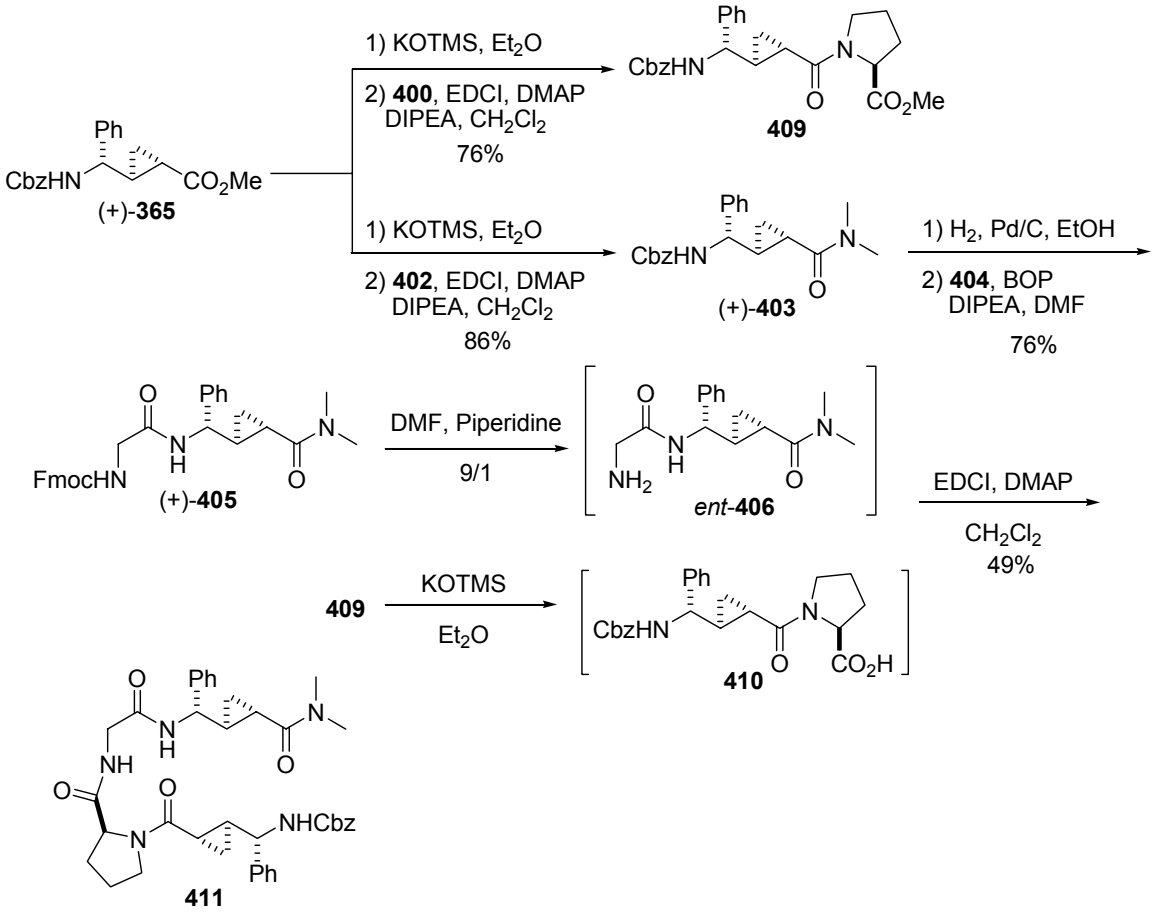


408

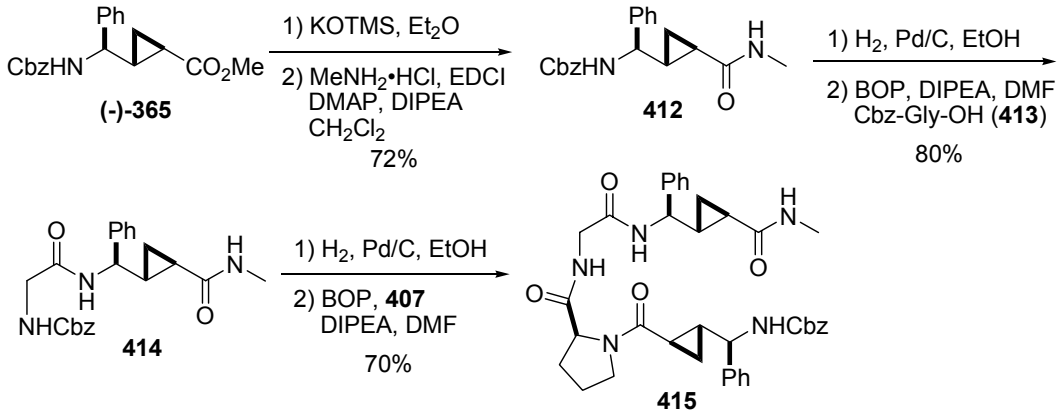
Figure 2.11. Stereoview of the Chem3D representation of the x-ray crystal structure of **408**[298]

We thought it might be possible to favor interaction between the ΔPhg residues by incorporating the enantiomeric amino acid ((+)-**365**) while keeping the β-turn motif constant (Scheme 2.20). A sample of (+)-**365** was divided into two portions and after saponification with KOTMS in Et_2O, the crude acid was coupled with **402** and **400** to give peptides (+)-**403** and **409** in 86% and 76% yield, respectively. Cbz-deprotection (H_2, Pd/C, MeOH), coupling with **404** (BOP, DIPEA, 76%) and Fmoc-deprotection afforded the intermediate amine *ent*-**406**. Saponification of **409** and coupling with *ent*-**406** (EDCI, DMAP) afforded the tetrapeptide **411** in modest yield (49%).

[298] See Appendix G for crystal coordinates.



Scheme 2.20. Synthesis of tetrapeptide **411**

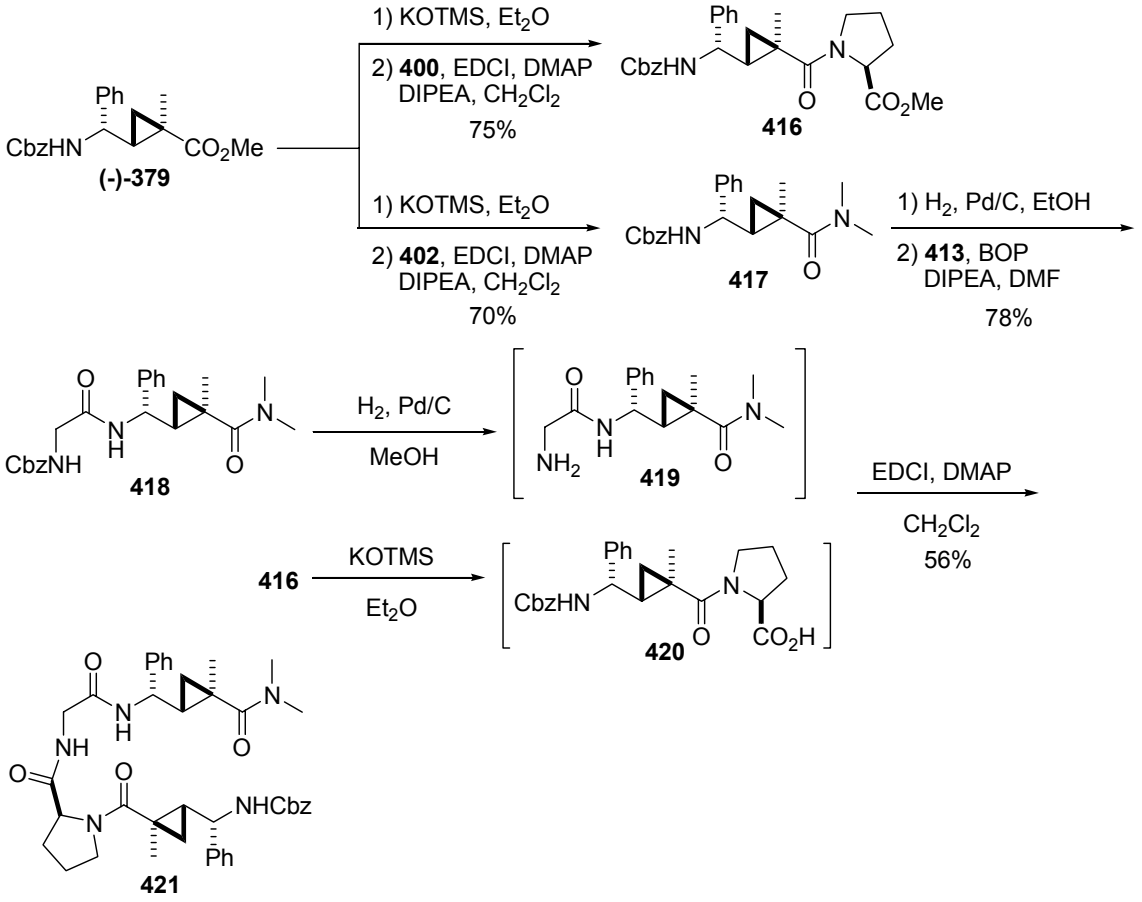


Scheme 2.21. Synthesis of tetrapeptide **415**

To examine the effect of the amide at the C-terminus and potentially favor an alternate hydrogen bonding motif between the C- and N-termini, we prepared C-terminal capped methyl

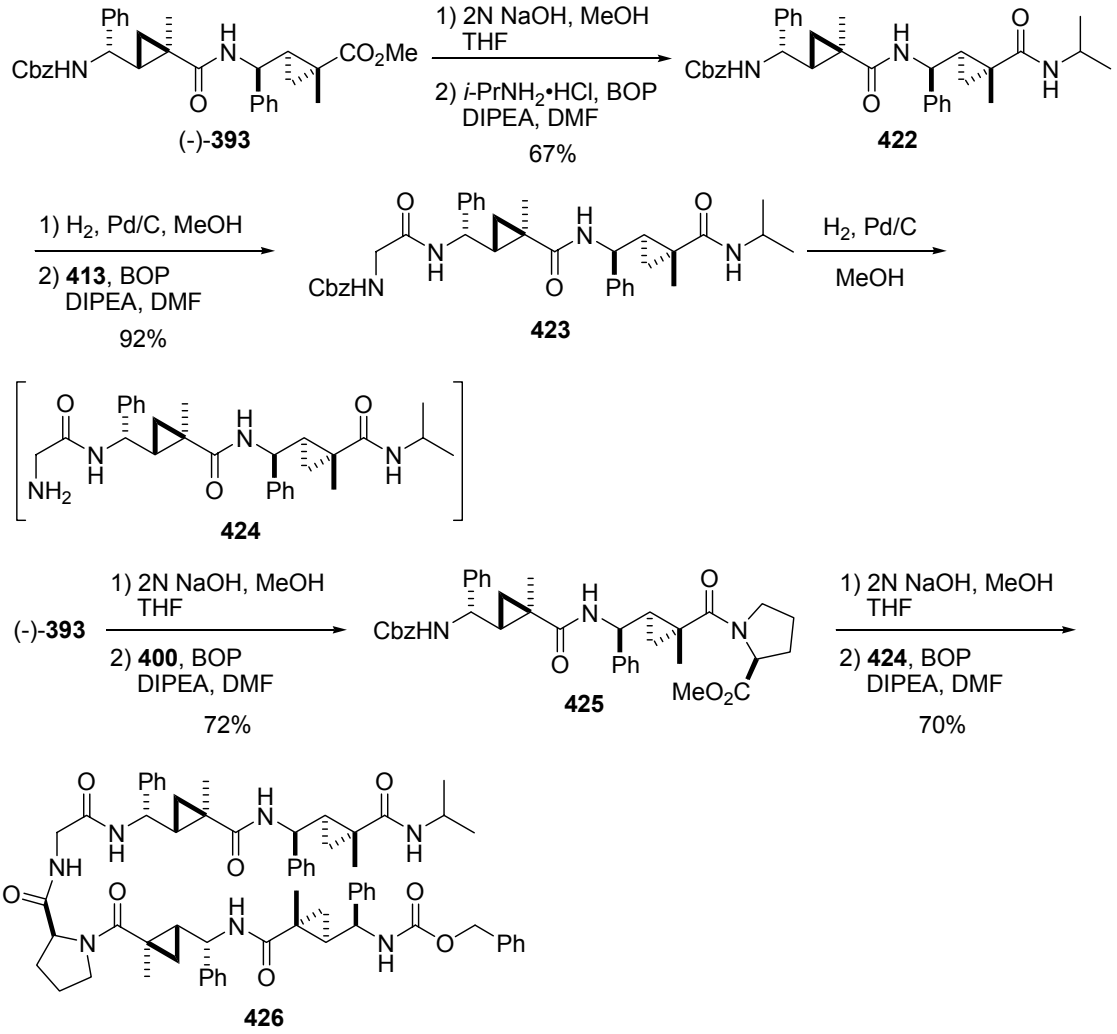
amide **415** (Scheme 2.21). Saponification of (-)-**365** (KOTMS, Et_2O) and coupling with $MeNH_2$•HCl afforded **412** in 72% yield. Deprotection of the benzyl carbamate and coupling with Cbz-Gly-OH (BOP, DIPEA, DMF) gave 80% of dipeptide **414**. Hydrogenolysis of the benzyl carbamate followed by BOP coupling with **407** (see Scheme 2.19) in the presence of DIPEA afforded the desired tetrapeptide **415** in good yield (70%).

On the basis of the solid state analysis of the isopropylamide of (+/-)-**379** (Figure 2.9), a β-hairpin containing two $^{\alpha}$MeΔPhg residues was prepared (Scheme 2.22). The proline and methyl amide peptides were prepared in good yields using analogous protocols to those seen in the previous schemes. Deprotection of the benzyl carbamate of **417** and coupling with **413** (BOP, DIPEA, DMF) afforded the depeptide **418** (78%). Hydrogenolysis of the Cbz group and coupling (EDCI, DMAP, CH_2Cl_2) with acid **421** afforded tetrapeptide **421** in 56% yield.



Scheme 2.22. Synthesis of tetrapeptide **421**

The final β-hairpin that was prepared was an extended version of **421** composed of two $^{\alpha}$MeΔPhg dimers linked via a Pro-Gly dipeptide (Scheme 2.23). Beginning with dipeptide (-)-**393** (see Scheme 2.17), saponification (2 N NaOH, MeOH/THF) and coupling with i-$PrNH_2$•HCl (BOP, DIPEA, DMF) afforded isopropylamide **422**. Hydrogenolysis of the Cbz group and coupling with **413** afforded tripeptide **423** in 92% yield. Deprotection of the benzyl carbamate afforded the amine **424** required for segment condensation. Dipeptide (-)-**393** was saponified (2 N NaOH, MeOH/THF) and coupled with **400** in the presence of BOP and DIPEA to give 72% of tripeptide **425**. Deprotection of methyl ester and coupling with **424** (BOP, DIPEA, DMF) afforded the desired hexapeptide **426** in 70% yield.[299]



Scheme 2.23. Synthesis of hexapeptide **426**

[299] We have been able to grow crystals of **426** from CH_2Cl_2/toluene and EtOAc/hexanes, however, the structure could not be solved.

2.3 Structural Analyses of Cyclopropyl Peptides

2.3.1 Molecular Modeling

The molecular modeling (MM2*) of our simple phenylalanine derivatives **388** and **389** (Figure 2.12) led to what appears to be a matched and mismatched set of dipeptides. A tight pseudo-β-turn (Table 2.3) is well conserved for the low energy conformers of **388**, however the lowest energy conformations of **389** display a much more disordered arrangement, although the pseudo-β-turn family is also present and is represented by the lowest energy conformer. We have observed two different pseudo-β-turn structures (type I and II) which have major differences in the δ and ψ dihedral angles. The NH-CO hydrogen bond is explicitly conserved in all of the minimum energy conformations which incorporate a pseudo-β-turn motif. Interestingly, 110 and 155 unique conformations of **388** and **389** fell within an imposed 5 kJ/mol window of the lowest energy conformation.[300,301]

The phenylalanine derivatives of $^{\alpha}$MeΔPhg amino acids also have a noticeable preference for the formation of a pseudo-β-turn (Figure 2.13). The energy well is significantly restricted compared with **388** and **389**, however 50 and 25 structures were found within our imposed 5 kJ/mol cut-off for **391** and **392** respectively. The proclivity for turn formation appears to be favored for the *L*-amino acid, though the overlay for the *D*-amino acid is also quite good, there is considerably more disorder at the termini. Unfortunately, we were unable to confirm this preferred turn conformation for **392** using NMR techniques (vide infra). For both NH resonances, the temperature shift coefficients were >7 ppb/K in DMSO-d_6. It is also interesting to note that **391** was used to confirm the absolute stereochemistry of our resolved amino acids, and an extended structure was favored in the solid state, although this preference could be attributed to crystal packing forces favoring intermolecular interactions.

[300] A Monte-Carlo search routine was used to find the lowest energy conformations and only those within 5 kJ/mol of the lowest energy conformer were included in the overlay representations for all the peptides presented herein. For **388**, **389**, **391**, **392**, **397**, **408**, **411**, **415**, **421** and **422**, 10,000 conformations were analyzed. In the case of **426**, 25,000 structures were analyzed.

[301] For both **388** and **389**, the lowest energy conformation is the pseudo-β-turn.

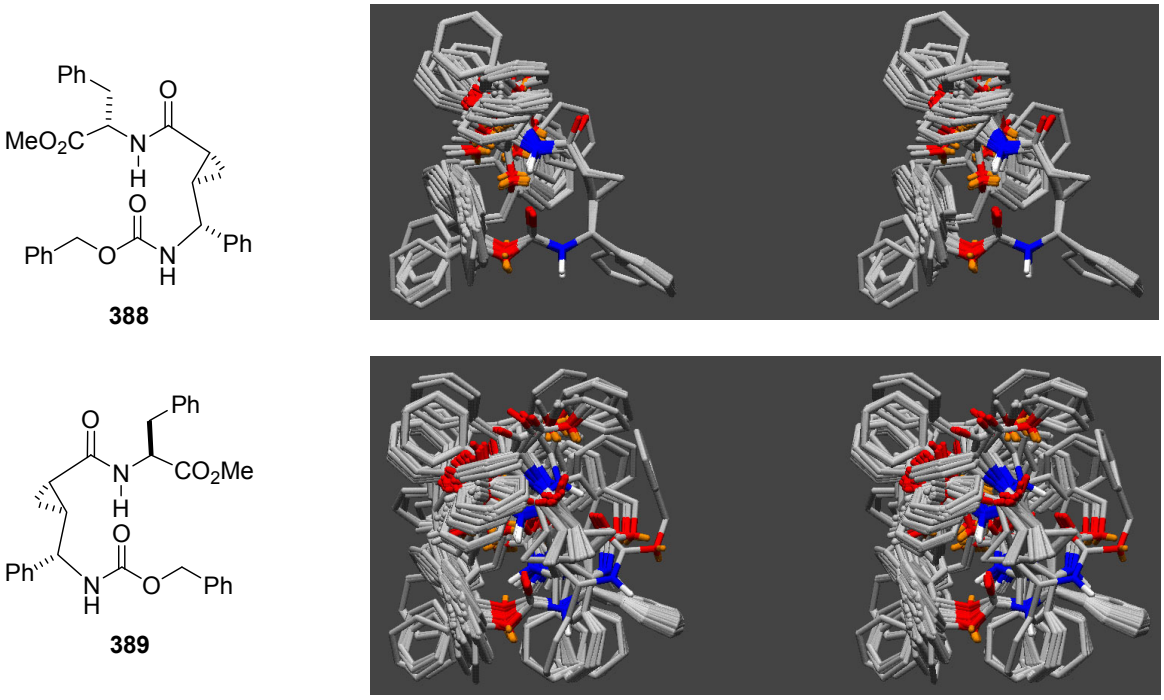
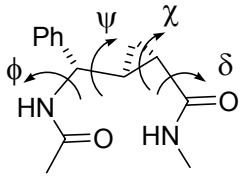


Figure 2.12. Stereoview of the Macromodel-generated overlays of the lowest energy conformations for dipeptides **388** and **389**

Table 2.3. Dihedral angles of the pseudo β-turns observed for the lowest energy conformers



pseudo β-turn

	δ (°)	χ (°)	ψ (°)	ϕ (°)	NH-CO distance (Å)	type[a]
388	76.3	-144.8	104.0	-49.2	1.828	I
389	-88.4	136.7	-103.9	67.3	1.907	I’
391	73.5	-146.9	104.0	-37.0	1.849	I
392	-80.4	144.9	-103.5	37.1	1.843	I’
397	80.1	-143.3	109.2	-43.6	1.873	I
422	63.4/54.0	-144.6/-146.4	49.0/47.4	40.1/39.7	1.851/1.857	II/II
426	67.1/81.6	-144.8/-142.6	48.8/109.1	41.8/-44.0	1.862/1.854	II/I

[a]A type I’ turn is enantiomeric to a type I turn.

The linear peptides **397** and **422** also demonstrate a preference for a β-turn like structure about the *trans*-cyclopropane residue. Interestingly, the lowest energy structure of **422** (of 28 total) consists of two pseudo-β-turns motifs forming a helical strand (Figure 2.14). However, as we can see in the overlay structure, there is considerable disorder in the *C*-terminal residue and the helical strand family of structures does not represent the majority of conformations. The lowest energy conformation of **397** is a β-hairpin, although there are two major families of structures; approximately half of the structures (out of 41) pick up the second hydrogen bond (as drawn), while the NH-carbonyl interaction is not observed for the remaining conformations.

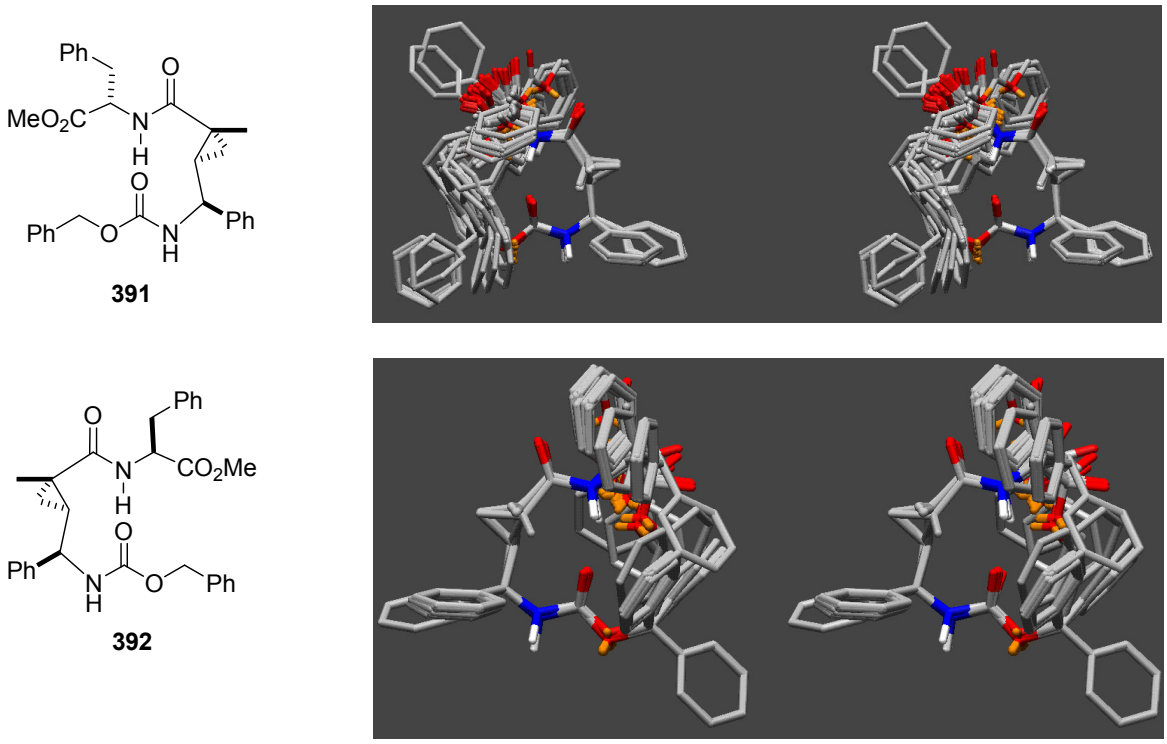


Figure 2.13. Stereoview of the Macromodel-generated overlays for the lowest energy conformations of dipeptides **391** and **392**

On the basis of our modeling work, these β-hairpin mimics are predicted to be very conformationally mobile in solution. For all examples of $H_2\Delta$Phg-containing tetrapeptides **408** (Figure 2.15), **411** (Figure 2.16), and **415** (Figure 2.17), two main families of structures are observed about the Pro-Gly linkage. In one family, a turn is initiated at the Pro-Gly linkage, however, the i/(i+3) hydrogen bond is not explicitly conserved. Alternatively, two successive γ-turns were found. The conformational mobility may be attributed to the conformationally

flexible Gly residue causing considerable disorder in the *C*- and *N*-terminal residues. Perhaps a more judicious choice of amino acid in place of Gly (for example *D*-Phe) may impart a more rigidly controlled β-turn to these peptides. Schreiber and co-workers report that a vinylogous amino acid derivative similar to **408** affords a β-hairpin in solution.[238] However, the only experiment that is used to support this conjecture is the dependence (or lack thereof) of NH chemical shifts with dilution in $CDCl_3$. Our model peptides (ie, **366**, **372**, **380** and **391**) have structural properties analogous to those prepared by Schreiber and co-workers, and it was anticipated that the β-hairpin structure would similarly be favored in **408**. In the absence of

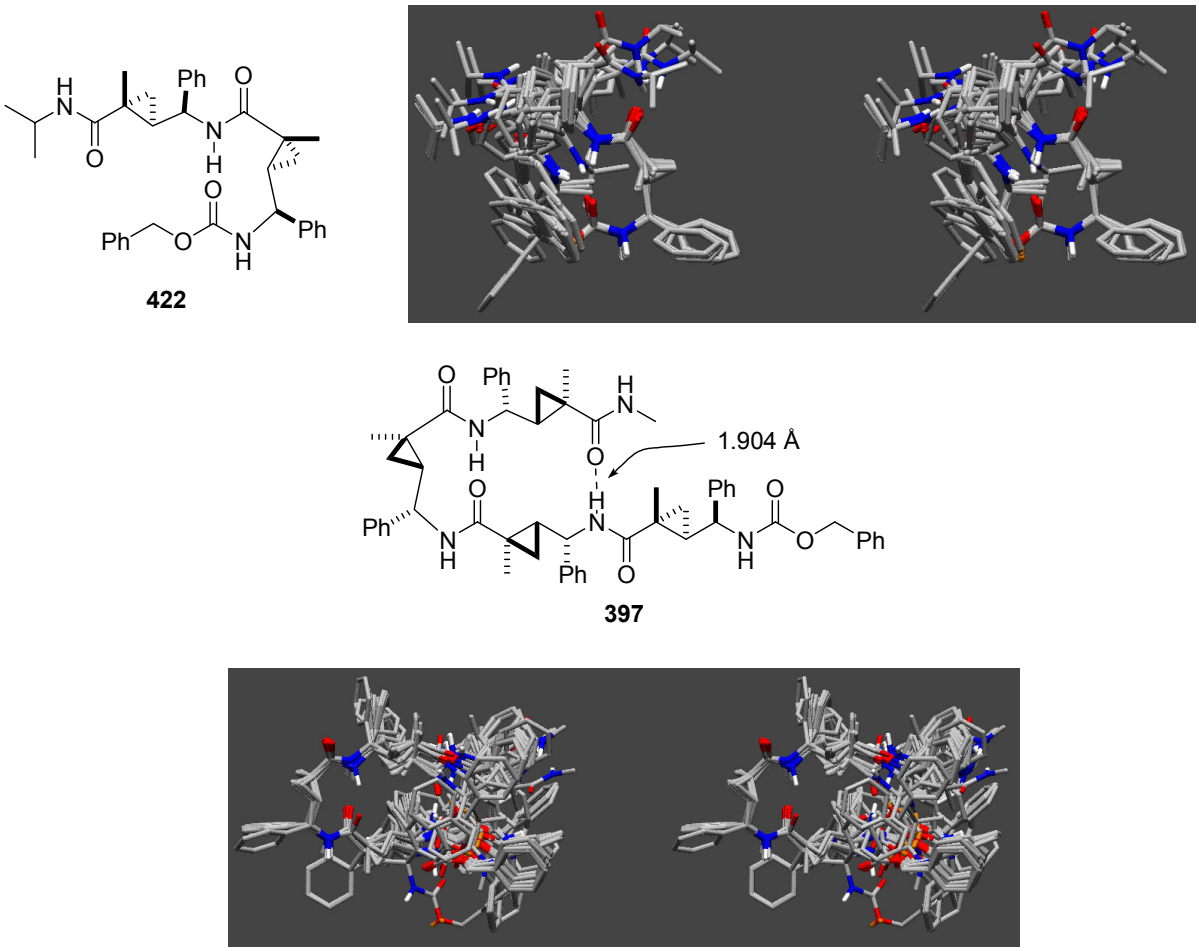
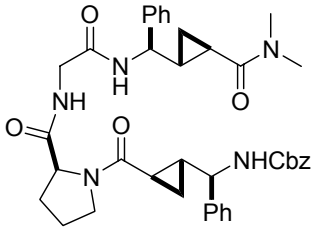


Figure 2.14. Stereoview of the Macromodel-generated overlays of the lowest energy conformations of the oligopeptides **422** and **397**

further experimental evidence to support the secondary structural claims for the vinylogous peptides, we must conclude that the cyclopropyl substitution drastically effects the overall conformation of tetrapeptide **408**. At this stage, β-hairpins **411** and **415** were prepared in hopes of reversing this trend. However, we have been unable to grow crystals of these compounds and the solution hydrogen bonding patterns are not unlike those observed for compound **408**.



408

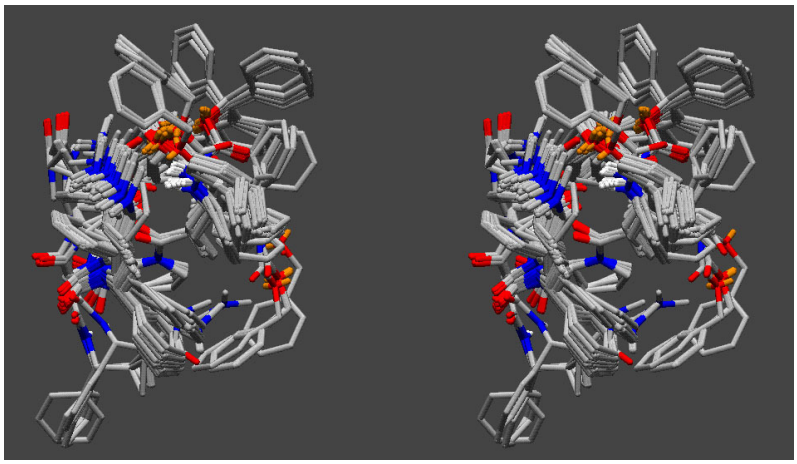
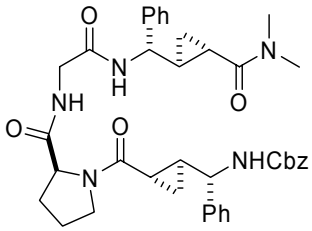


Figure 2.15. Stereoview of the Macromodel-generated overlay of the lowest energy conformations for tetrapeptide **408**



411

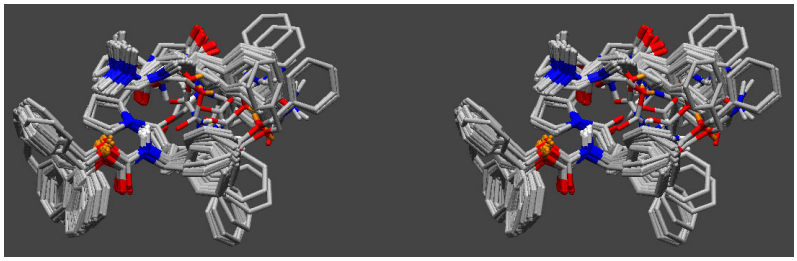


Figure 2.16. Stereoview of the Macromodel-generated overlay of the lowest energy conformations for tetrapeptide **411**

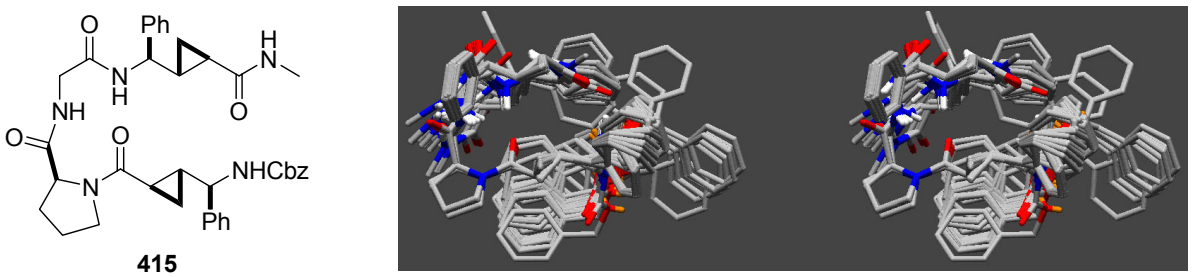


Figure 2.17. Stereoview of the Macromodel-generated overlay of the lowest energy conformations for tetrapeptide **415**

On the basis of our conformational analysis, of all β-hairpin mimics that we have prepared, tetrapeptide **421** appears to adopt the most stable β-hairpin structure (Figure 2.18). The backbone of the β-turn is well conserved in all of the calculated low energy structures and while there is variation in the *N*- and *C*-terminal residues, two major families of structures are observed. Both of these conformational families have a hydrogen bonding interaction between the *C*- and *N*-terminal residues. The presence of the closed β-hairpin indicates that the cyclopropyl amino acid residues play a critical role in the stabilization of this secondary structural motif since the Pro-Gly linkage present in **408**, **411** and **415** was in itself insufficient to nucleate the hairpin structure.

The hexapeptide **426** is simply an extended version of tetrapeptide **421** and we anticipated that we should be able to observe an extended β-hairpin. In fact, after conformational searching (25,000 structures), only four conformations fell within 5 kJ/mol of the minimum energy conformation. Of the four structures, the three lowest energy conformations are nearly super-imposable, adopting the general structure shown in Figure 2.19. This family of conformers forms an extended strand of hydrogen bonded turns initiated at the proline residue with two γ-turns followed by the pseudo-β-turn that has been found in a the majority of structures calculated thus far. Interestingly, the *C*-terminal residue also appears to participate in a bifurcated hydrogen bonding interaction with the carbonyl of the glycine residue. The *N*-terminal residue is involved in a pseudo-β-turn conformation which does not appear to interact with the main strand. The fourth conformation (4.9 kJ/mol above the minima) adopts a β-turn about the Pro-Gly linkage as was observed for **421**. The *C*-terminal residue (^{i}Pr amide) is

arranged in a pseudo-β-turn and positions the terminal NH within hydrogen bonding contact of the Cbz carbonyl group.

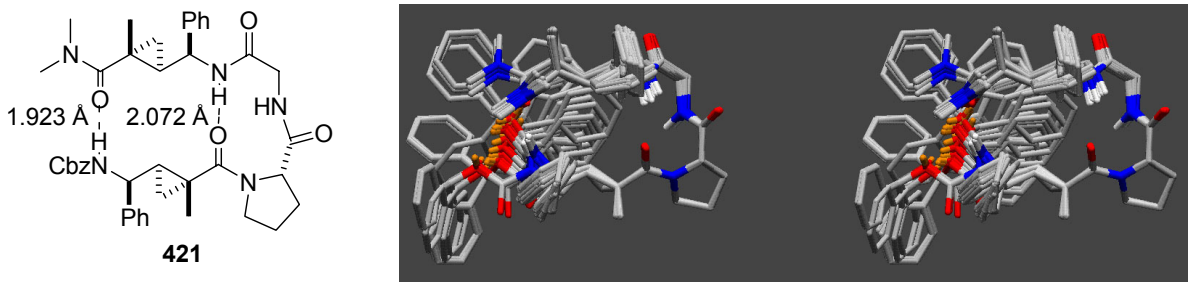
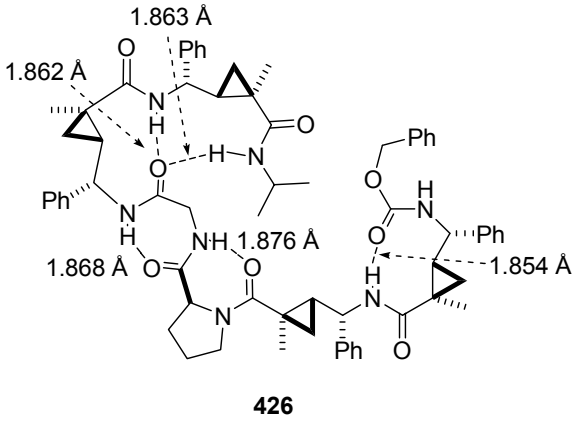


Figure 2.18. Stereoview of the Macromodel-generated overlay of the calculated lowest energy structures for β-hairpin **421**



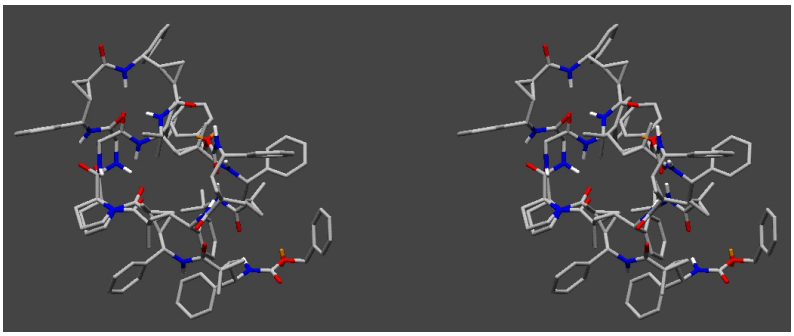


Figure 2.19. Stereoview of the Macromodel-generated overlay of the lowest energy conformations of **426**

2.3.2 Solution Studies of Oligopeptides Containing Cyclopropyl Amino Acids

Of the larger peptides that we have prepared, we have only been able to obtain crystals suitable for x-ray diffraction studies for dipeptide **391** and tetrapeptide **408**. In order to evaluate the secondary structures formed by our peptide mimetics, we decided to attempt structural studies in solution using NMR and circular dichroism. NMR studies of peptides at variable temperatures can provide a wealth of structural information and coupled with precise nOe measurements, a family of solution structures can be generated. In particular, the temperature dependence of amide NH chemical shift can provide valuable information concerning their availability for intermolecular hydrogen bonding with solvent.[302,303] Typically, these values range from 0 to -8 ppb/K in DMSO; a small co-efficient (0 to -3 ppb/K) is indicative of a proton which is strongly shielded from solvent exposure; an intermediate value (-3 to -4.5 ppb/K) indicates moderate shielding whereas values from -4.5 to -8 ppb/K indicate that the proton is exposed to the bulk solvent.[304]

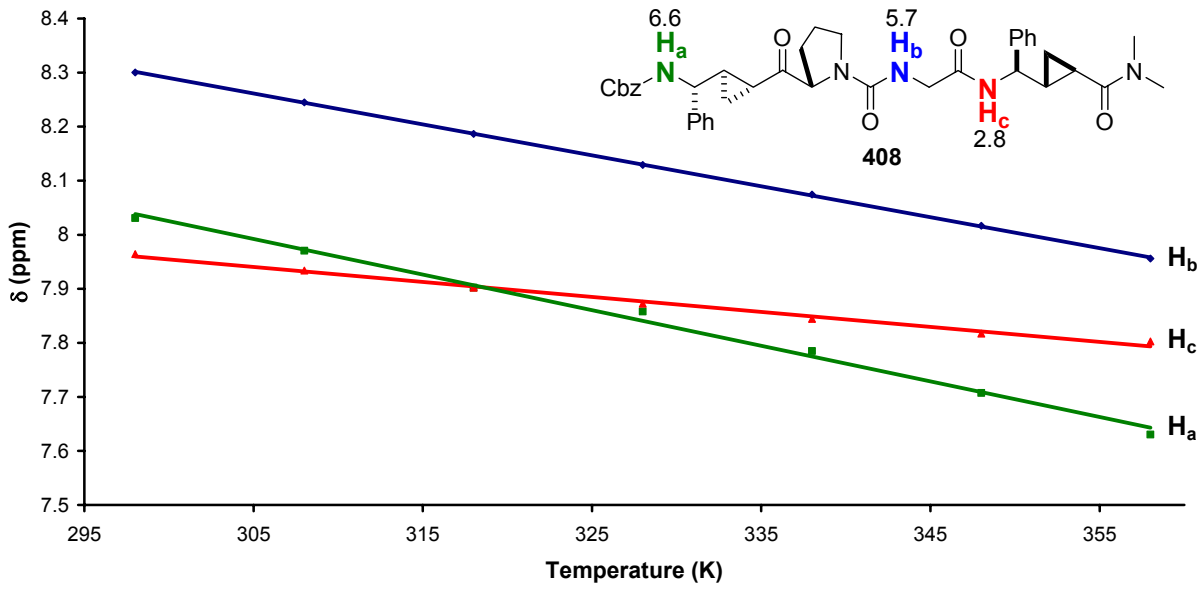


Figure 2.20. Amide proton chemical shift dependence on temperature for a 5.0 mM solution of tetraapeptide **408** in DMSO-d_6

[302] For the interpretation of temperature shift coefficients in polar aprotic solvents such as DMSO-d_6, see Smith, J. A.; Pease, L. G. *Crit. Rev. Bioch.* **1980**, *8*, 315.
[303] For the interpretation of temperature shift coefficients in non-polar solvents such as $CDCl_3$, see Stevens, E. S.; Sugawara, N.; Bonora, G. M.; Toniolo, C. *J. Am. Chem. Soc.* **1980**, *102*, 7048.
[304] Imperiali, B.; Fisher, S. L.; Moats, R. A.; Prins, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 3182.

We measured temperature shift coefficients for a number of oligopeptides and plotted the amide NH chemical shift vs. temperature for each amide in the peptide. In all but one case (**426**), all NH resonances could be assigned using a combination of 2D-NMR techniques (COSY, HMQC and HMBC). For example, the NH chemical shifts for **408** were measured from 298 K to 358 K in 10 K increments (Figure 2.20, entry 1, Table 2.4). Using linear regression analysis, the slope of the correlation between chemical shift and temperature represents the temperature shift coefficient for the amide NH. From this plot, we can see that only the NH of the *C*-terminal residue is involved in intramolecular hydrogen bonding interactions. The diastereomeric tetrapeptide, **411** (Table 2.4, entry 2) exhibits a similar pattern where the β-turn has been conserved, yet there is no evidence for attractive interactions between the terminal residues. It is interesting to note that the local conformational preference for the β-turn structure has been observed in the x-ray structure of **408** (Figure 2.11) and in the NH chemical shift correlation experiments for **408** and **411**. However, given that modeling indicates potential for γ-turns about the Pro-Gly linkage, we can not rule out the possibility that the observed low temperature shift co-efficients (<3.5 ppb/K) are part of a γ-turn motif. The methylamide-capped tetrapeptide **415** (Table 2.4, entry 3) was prepared in the hope of picking up an alternate interaction between the *C*- and *N*-terminal residues. In fact, not only is hydrogen bonding not observed between the termini, but this change drastically affected the overall conformation of the molecule and the β-turn is no longer present. On the basis of molecular modeling, the $^{\alpha}$MeΔPhg-derived peptide **421** was predicted to prefer a conformation consistent with a β-hairpin. Gratifyingly, the temperature shift co-efficients for both the Gly amide NH (i+3) and the *N*-terminal carbamate NH (i) are <3.5 ppb/K providing strong evidence for the formation of a stabilized minimal β-hairpin motif in DMSO solution. Unfortunately, we were unable to corroborate this evidence with long range NOE data, and attempts to crystallize **421** have been unsuccessful to date. The hexapeptide **426** could not be fully assigned by 2D-NMR techniques due to overlapping signals in the cyclopropane region. However, the temperature shift coefficients do not indicate an extended β-hairpin as we had hoped (Table 2.4, entry 5). Unfortunately, only the (i+3) residue appears to be involved in a hydrogen bond, although all of the coefficients are lower than previously observed (<5.6 ppb/K) which may indicate that the preferred conformation easily unfolds to expose the amide bonds with increased temperature.

Table 2.4. Temperature shift coefficients for 5.0 mM solutions in DMSO-d_6

		observed temperature shift coefficients (ppb/K)[a]					
entry	compound	i-1[305]	i	i+2	i+3	i+4	i+5
1	**408**	n/a	6.6	5.7	**2.8**	n/a	n/a
2[b]	**411**	n/a	7.5	7.2	**3.3**	n/a	n/a
3[b]	**415**	n/a	7.0	5.9	6.4	7.2	n/a
4[b]	**421**	n/a	**3.1**	5.4	**2.5**	n/a	n/a
5[b]	**426**[c]	5.6	4.9	5.6	**2.1**	4.5	5.0
6[b]	**422**[d]	7.6	7.2	7.0	n/a	n/a	n/a
7[b]	**392**[d]	7.7	7.6	n/a	n/a	n/a	n/a

[a]Absolute values; [b]See Appendix I for the chemical shift temperature correlations for entries 2-7; [c]The i and i+4 NH resonances could not be unambiguously assigned using 2D-NMR; [d]The temperature shift coefficients for **422** and **392** are given beginning with the *N*-terminal residue.

Table 2.5. Circular dichroism peaks in MeOH (0.2 mM)

Compound	λ (nm)	$[\theta]\bullet 10^{-3}\bullet cm^2\bullet dmol^{-1}$
388	215	40.8
389	221	18.5
391[a]	--	--
392	219	25.0
397	217	-83.2
422	217	-56.4
408	213	42.9
411[a]	--	--
415	229	11.5
421	230	9.29
426	219	-74.4

[a]A distinct transition was not observed.

On the basis of the circular dichroism data, we can conclude that the structures of **408** and **415** are similar in MeOH solution, while the CD data seems to indicate a random coil for both **411** and **421**. The random orientation of **411** is in accord with our molecular mechanics calculations while the data for **421** is puzzling and is not in agreement with the modeling or variable temperature NMR data. It is possible that the relatively flat curve for **421** is the result of the additive effects of two opposing Cotton effects.

[305] The residue number was assigned on the basis of the β-turn where the Pro residue is i+1, Gly i+2, etc.

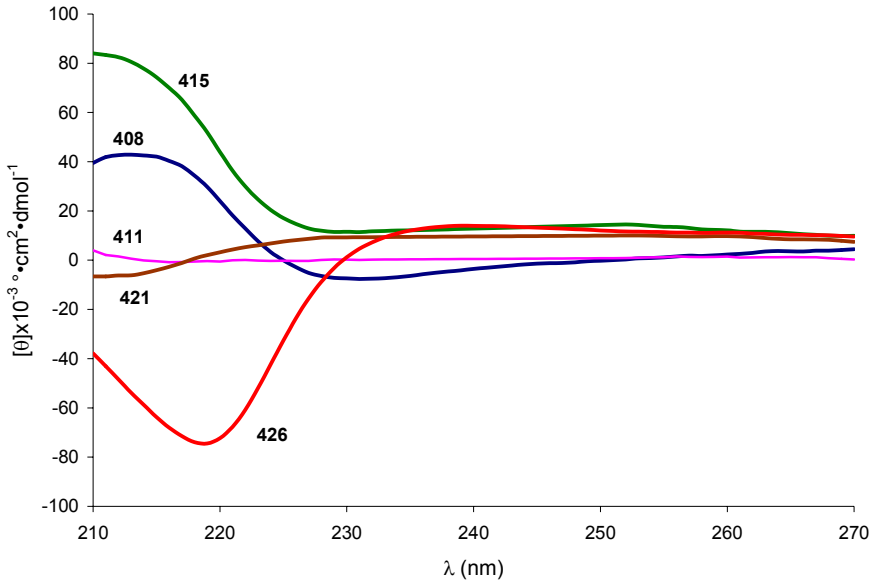


Figure 2.21. Circular dichroism spectra for β-hairpin peptides **408**, **411**, **415**, **421** and **426**[306]

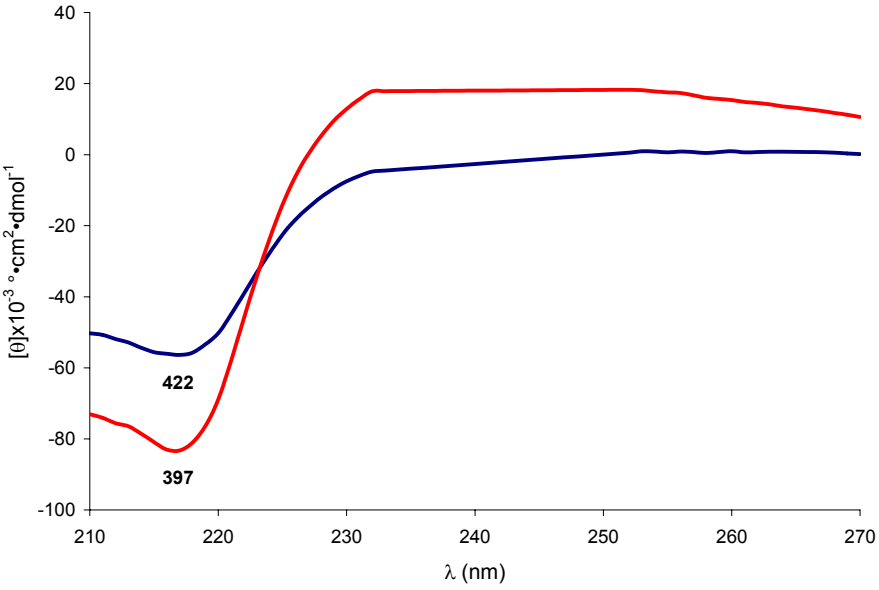


Figure 2.22. Circular dichroism spectra for peptides **397** and **422**[306]

[306] Circular dichroism spectra were measured for a 0.2 mM solution in MeOH. Shown are 5 averaged scans at 21 °C.

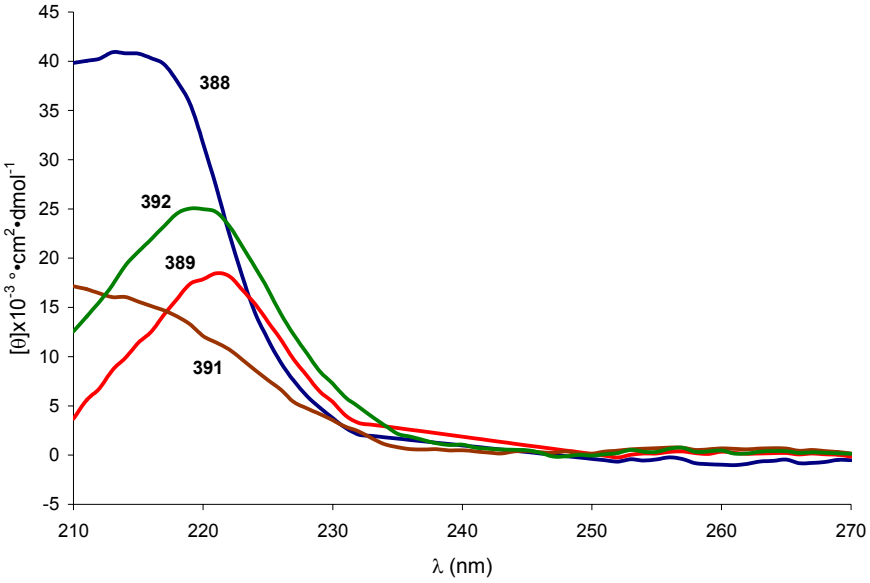


Figure 2.23. Circular dichroism spectra for phenylalanine derivatives **388**, **389**, **391** and **392**[306]

Finally, the temperature shift co-efficients observed for **422** and **392** do not support the calculated preferred conformations (Table 2.4, entry 6 and 7), and may indicate a preference for an extended structure for these small peptides in solution. Interestingly, there is excellent correlation between the CD spectra of **422** and **397** indicating that these two peptides may share similar conformations in solution (Figure 2.22). Likewise, the phenylalanine derivatives **389** and **392** have very similar CD spectra (Figure 2.23), and while this seems to agree very well with our calculated structures, we were unable to observe the intramolecular hydrogen bonding for **392** in DMSO (Table 2.4, entry 7).

At this stage, the structural information that we have been able to collect thus far tends to indicate a preference for extended structures in the solid state, while our calculations have predicted a strong preference for reverse turn-like conformations. In the solid state, the crystal packing forces and the stabilization via intermolecular interactions may be the driving force for the formation of the observed sheet-like arrangements. However, we have not been able to unambiguously determine the conformational preference in solution.

2.4 Conclusions

We have achieved a concise synthesis of a family of cyclopropyl amino acids ($H_2\Delta$Phg, $^{\alpha}$MeΔPhg, $^{\beta}$MeΔPhg) in 6-7 steps and 30-45% overall yield highlighting some of the methodology presented in the first chapter of this dissertation. Simple amide derivatives were found to fold into stable sheet-like structures in the solid state. After this preliminary evaluation, the $H_2\Delta$Phg and $^{\alpha}$MeΔPhg scaffolds were resolved via fractional crystallization for further assessment of their potential to induce extended structures in oligopeptides. A number of linear oligopeptides were prepared, however, we were unable to grow crystals suitable for x-ray diffraction studies of anything larger than a dimer. Circular dichroism studies of these linear peptides coupled with molecular modeling allowed for a correlation of the observed CD spectra with the calculated conformational minima.

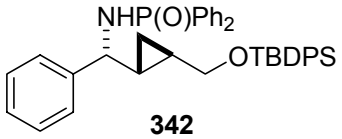
Solution studies were also undertaken for the designed β-hairpin structures **408**, **411**, **415**, **421** and **426** and while the built-in β-turn was observed by variable temperature NMR studies in nearly every case, only the $^{\alpha}$MeΔPhg scaffold picked up the hydrogen bonding contact between the *C*- and *N*-termini. Similar to the studies of the linear peptides, the CD spectra of the minimal β-hairpins were interpreted using molecular modeling.

Finally, the isopropyl amide **380** has been found to be a pregnane X receptor agonist which exhibits differential activity between human and mouse based assays. In fact, (+)-**380** has been found to be more active in hPXR whereas (-)-**380** was a better agonist for mPXR. Similarly, phosphinamide **363** has been shown to suppress pre-mRNA splicing of CD45. Unfortunately, the molecular target of **363** is unclear, although it appears to act via a novel mechanism/target. Focused libraries of analogs of **363** and **380** will improve our understanding of the origin of the species-dependent stereoselectivity of **380** and hopefully improve activity for RNA splicing as well as allow the determination of the molecular target.

Despite the conformational rigidity of our new amino acid scaffold, the rational prediction of secondary structure remains difficult as the peptides appear to possess significant conformational freedom. The most promising aspect of this work lies in the continued evaluation of cyclopropyl amino acid derivatives in a biological context. An expanded library of analogs related to amino acids other than phenylglycine should be evaluated and could lead to the discovery of interesting lead structures.

2.5 Experimental Part

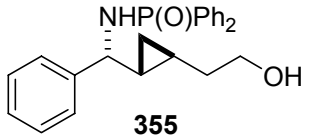
General. All general comments from Chapter 1.6 pertain also to this experimental section. CD spectra were recorded using a JASCO 715 spectrometer.



342

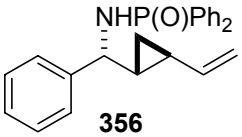
***N*-(*R**)-{((1*R**,2*R**)-2-(*tert*-Butyldiphenylsilyloxymethyl)cyclopropyl)(phenyl)methyl}-*P*,*P*-diphenylphosphinamide** (**342**). To a suspension of Cp_2ZrHCl (0.69 g, 2.7 mmol) in dry CH_2Cl_2 (5.0 mL) was added **341** (0.79 g, 2.7 mmol). The reaction mixture was stirred for 10 min, cooled to -78 °C, treated with Me_2Zn (1.3 mL, 2.7 mmol, 2.0 M in toluene) and warmed to 0 °C. After addition of **21** (0.27 g, 0.89 mmol), the mixture was heated at reflux for 12 h, cooled to 0 °C, treated with a solution of $Zn(CH_2I)_2$•DME[307] (4.5 mmol in 2.5 mL CH_2Cl_2) and stirred for 5 h. The solution was quenched with sat. NH_4Cl, diluted with EtOAc and filtered through a mixture of Celite and SiO_2 (~1:1). The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on SiO_2 (2:3, hexanes/EtOAc) to afford **342** (0.30 g, 56%) as a colorless foam: IR (neat) 3189, 3070, 3028, 2930, 2857, 1590, 1471, 1455, 1438, 1428, 1190, 1111 cm^{-1}; ^1H NMR δ 7.93-7.86 (m, 2 H), 7.75-7.62 (m, 7 H), 7.47-7.33 (m, 12 H), 7.31-7.24 (m, 4 H), 3.80 (dt, *J* = 10.0, 7.9 Hz, 1 H), 3.63 (dd, *J* = 10.6, 5.4 Hz, 1 H), 3.42 (dd, *J* = 10.6, 6.2 Hz, 1 H), 3.32-3.28 (m, 1 H), 1.23-1.08 (m, 2 H), 1.01 (s, 9 H), 0.51 (dt, *J* = 8.5, 5.1 Hz, 1 H), 0.42 (dt, *J* = 8.5, 5.2 Hz, 1 H); ^{13}C NMR δ 143.35, 143.30, 135.53, 135.50, 133.82, 132.30, 132.17, 131.97, 131.85, 131.62, 131.59, 131.41, 129.48, 128.37, 128.20, 128.13, 127.96, 127.53, 126.96, 126.79, 66.15, 58.16, 26.83, 24.76, 24.68, 20.33, 19.09, 8.45; MS (ESI) *m/z* (intensity) 1253 ($[2M+Na]^+$, 23), 1231 ($[2M+H]^+$, 20), 638 ($[M+Na]^+$, 35), 616 ($[M+H]^+$, 100), 538 (29); HRMS (ESI) *m/z* calculated for $C_{39}H_{43}NO_2PSi$ (M+H) 616.2801, found 616.2799.

[307] $Zn(CH_2I)_2$•DME complex was prepared by dropwise addition of CH_2I_2 (0.72 mL, 8.9 mmol) to a cooled (-20 °C) solution of Et_2Zn (0.55 g, 4.5 mmol) and DME (0.46 mL, 4.5 mmol) in dry CH_2Cl_2 (2.5 mL). The solution was stirred for 10 min and added to the reaction mixture via canula.



355

***N*-(*R**)-(((1*R**,2*S**)-2-(2-hydroxyethyl)cyclopropyl)(phenyl)methyl)-*P*,*P*-diphenylphosphinamide** (**355**). **General Protocol N**. To a solution of **177** (7.0 g, 11 mmol) in dry THF (0.11 L) was added AcOH (1.3 mL, 22 mmol) and TBAF (22 mL, 22 mmol, 1.0 M in THF). The reaction mixture was stirred for 12 h, quenched with sat. NH_4Cl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (65:35, CH_2Cl_2/acetone containing 1% v/v Et_3N) to afford **355** (3.3 g, 76%) as a colorless foam: IR (neat) 3218, 3048, 2924, 2863, 1438, 1180, 1123, 1111 cm^{-1}; ^1H NMR δ 7.92-7.81 (m, 4 H), 7.50-7.25 (m, 11 H), 4.68 (bs, 1 H), 3.84-3.73 (m, 3 H), 3.28-3.15 (m, 1 H), 2.18-2.07 (m, 1 H), 1.32-1.22 (m, 1 H), 1.09-1.00 (m, 1 H), 0.80-0.69 (m, 1 H), 0.42-0.30 (m, 2 H); ^{13}C NMR δ 143.76, 143.64, 133.68, 133.02, 132.89, 132.07, 132.02, 131.97, 131.78, 131.65, 131.46, 129.69, 128.63, 128.48, 128.44, 127.21, 126.11, 61.71, 61.20, 37.56, 28.01, 17.95, 12.23; MS (EI) *m/z* (intensity) 391 (M^+, 0.5), 306 (27), 255 (71), 216 (68), 201 (100), 143 (79), 125 (63); HRMS (EI) *m/z* calculated for $C_{24}H_{26}NO_2P$ 391.1701, found 391.1686.

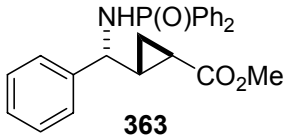


356

***N*-(*R**)-(Phenyl((1*R**,2*S**)-2-vinylcyclopropyl)methyl)-*P*,*P*-diphenylphosphinamide (356)**. **General Protocol O**. To a cooled (0 °C) solution of **355** (1.8 g, 4.6 mmol) and *o*-$NO_2C_6H_4SeCN$ (2.1 g, 9.2 mmol) in dry THF (75 mL) was added dropwise a solution of Bu_3P[308] (1.9 g, 9.2 mmol) in dry THF (10 mL). The reaction mixture was stirred for 1 h, quenched with sat. $NaHCO_3$ and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was dissolved in dry CH_2Cl_2 (0.10 L), cooled to -40 °C and treated with Na_2HPO_4 (3.3 g, 23 mmol) and *m*-CPBA (2.7 g, 11 mmol, ~70% w/w *m*-CPBA). The reaction mixture was stirred until the selenide was consumed (as judged by TLC analysis), treated with freshly distilled *i*-Pr_2NH (3.2 mL, 23 mmol), warmed to r.t. and stirred for 12 h. The solution was quenched with sat. $NaHCO_3$ and extracted with

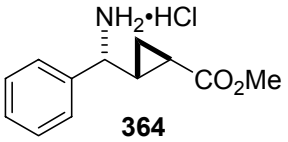
[308] Tri-*n*-butylphosphine was stored in a glove box.

EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (1:1, hexanes/EtOAc containing 1% v/v Et_3N) to afford **356** (1.5 g, 88%) as a colorless solid: mp 166.8-169.2 °C (hexanes/EtOAc); IR (KBr) 3198, 3076, 3026, 3000, 2871, 1636, 1456, 1436, 1183, 1124, 1107 cm^{-1}; ^1H NMR δ 7.94-7.88 (m, 2 H), 7.77-7.71 (m, 2 H), 7.52-7.40 (m, 4 H), 7.35-7.22 (m, 7 H), 5.45-5.30 (m, 1 H), 5.03 (dd, *J* = 17.0, 0.8 Hz, 1 H), 4.84 (d, *J* = 10.2, 1.2 Hz, 1 H), 3.85 (app q, *J* = 8.8 Hz, 1 H), 3.40-3.35 (m, 1 H), 1.48 (septet, *J* = 4.8 Hz, 1 H), 1.36-1.27 (m, 1 H), 0.71 (dt, *J* = 8.5, 5.1 Hz, 1 H), 0.63 (dt, *J* = 8.5, 5.1 Hz, 1 H); ^{13}C NMR δ 143.08, 143.01, 140.18, 132.25, 132.22, 132.09, 132.00, 131.74, 131.71, 131.63, 128.50, 128.40, 128.33, 128.16, 127.20, 126.83, 112.38, 58.39, 28.60, 28.54, 22.09, 12.33; MS (EI) *m/z* (intensity) 373 (M^+, 6), 319 (50), 210 (100), 156 (30); HRMS (EI) *m/z* calculated for $C_{24}H_{24}NOP$ 373.1596, found 373.1604.



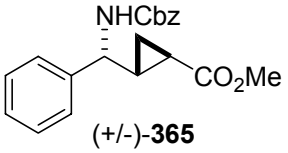
363

(1*R,2*R**)-Methyl 2-((*R**)-(diphenylphosphinoylamino)(phenyl)methyl)cyclopropanecarboxylate (Dpp-H_2ΔPhg-OMe) (363)**. **General Protocol P**. A solution of **356** (1.5 g, 4.0 mmol) in dry CH_2Cl_2 (0.10 L) was treated with a solution of NaOH (25 mL, 2.5 M in MeOH) and cooled to -78 °C. The reaction mixture was treated with a stream of O_3 (~4.5% v/v O_3 in O_2) for 6 h (until a faint blue color persisted), diluted with water and EtOAc and warmed to r.t. The mixture was extracted with EtOAc (3x) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated to afford **363** (1.6 g, quant) as a colorless solid which was used without further purification. An analytical sample was purified by crystallization from hexanes/EtOAc: mp 187.5-188.5 °C (hexanes/EtOAc); IR (KBr) 3211, 3051, 3007, 2948, 1713, 1438, 1213, 1176, 1121, 1110 cm^{-1}; ^1H NMR δ 7.94-7.88 (m, 2 H), 7.75-7.69 (m, 2 H), 7.55-7.42 (m, 4 H), 7.36-7.27 (m, 7 H), 3.87 (app q, *J* = 8.9 Hz, 1 H), 3.62 (s, 3 H), 3.35 (t, *J* = 7.5 Hz, 1 H), 1.97-1.88 (m, 1 H), 1.78 (dt, *J* = 8.5, 4.6 Hz, 1 H), 1.13 (dt, *J* = 8.8, 4.8 Hz, 1 H), 0.92-0.86 (m, 1 H); ^{13}C NMR δ 173.90, 142.38, 142.31, 132.30, 132.21, 132.07, 132.04, 131.92, 131.83, 131.80, 131.76, 131.73, 131.62, 128.63, 128.56, 128.40, 128.24, 127.58, 126.80, 57.52, 51.69, 29.08, 29.02, 20.07, 13.92; MS (EI) *m/z* (intensity) 405 (M^+, 2), 319 (41), 306 (46), 201 (100), 129 (16); HRMS (EI) *m/z* calculated for $C_{24}H_{24}NO_3P$ 405.1494, found 405.1484.



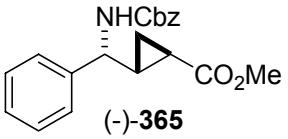
364

(1*R,2*R**)-Methyl 2-((*R**)-amino(phenyl)methyl)cyclopropanecarboxylate hydrochloride ($H_2\Delta$Phg-OMe•HCl) (364)**. **General Protocol Q**. To a cooled (0 °C) solution of **363** (1.6 g, 4.0 mmol) in MeOH (20 mL) was added a freshly prepared solution of HCl (20 mL, 1.0 M in MeOH). The reaction mixture was warmed to r.t., stirred for 12 h, and poured into dry Et_2O (~0.30 L). The suspension was cooled to 0 °C and filtered to afford **364** (0.74 g, 76%) as a colorless solid: mp 289.0-291.5 °C (dec., ether/MeOH); IR (KBr) 3419, 2963, 2875, 1719, 1605, 1507, 1458, 1371, 1239, 1213, 1172 cm^{-1}; ^1H NMR (CD_3OD) δ 7.49-7.43 (m, 5 H), 3.82 (d, *J* = 9.5 Hz, 1 H), 3.71 (s, 3 H), 2.05-1.95 (m, 2 H), 1.24-1.17 (m, 1 H), 1.08-1.02 (m, 1 H); ^{13}C NMR (CD_3OD) δ 173.55, 136.43, 129.48, 129.40, 127.21, 58.14, 51.57, 24.91, 20.10, 12.86.



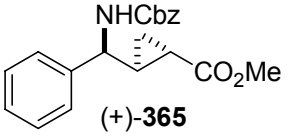
(+/-)-**365**

(+/-)-Cbz-$H_2\Delta$Phg-OMe ((+/-)-365). **General Protocol R**. To a cooled (0 °C) biphasic mixture of **364** (50 mg, 0.21 mmol) in EtOAc (1.0 mL) and H_2O (1.0 mL) was added $NaHCO_3$ (87 mg, 1.0 mmol) and Cbz-Cl (35 μL, 0.25 mmol). The reaction mixture was vigorously stirred for 2 h, diluted with H_2O and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (4:1, hexanes/EtOAc) to afford (+/-)-**365** (66 mg, 95%) as a colorless oil that solidified on standing: IR (neat) 3348, 3063, 3032, 2952, 1721, 1690, 1526, 1454, 1347, 1258, 1242, 1207, 1179 cm^{-1}; ^1H NMR δ 7.39-7.30 (m, 10 H), 5.20 (bs, 1 H), 5.17, 5.08 (AB, *J* = 12.2 Hz, 2 H), 4.32 (bm, 1 H), 3.69 (s, 3 H), 1.90-1.80 (m, 2 H), 1.29-1.23 (m, 1 H), 0.98-0.92 (m, 1 H); ^{13}C NMR δ 173.94, 155.70, 140.78, 136.28, 128.70, 128.48, 128.10, 128.04, 127.76, 126.51, 66.93, 57.45, 51.85, 27.29, 19.02, 13.78; MS (EI) *m/z* (intensity) 248 ($[M-C_7H_7]^+$, 2), 145 (22), 91 (100); HRMS (EI) *m/z* calculated for $C_{13}H_{14}NO_4$ ($M-C_7H_7$) 248.0923, found 248.0935.



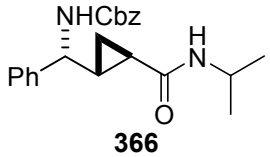
(-)-**365**

Cbz-*L*-H$_2$ΔPhg ((-)-365). According to the General Protocol R, **383** (80 mg, 0.22 mmol), $NaHCO_3$ (95 mg, 1.1 mmol) and Cbz-Cl (40 μL, 0.27 mmol) in EtOAc/H_2O (1:1, 4.0 mL) afforded (-)-**365** (69 mg, 90%) as a colorless solid: $[\alpha]_D$ -51.2 (*c* 0.92, $CHCl_3$).



(+)-**365**

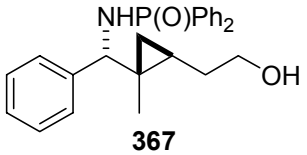
Cbz-*D*-H$_2$ΔPhg ((+)-365). According to the General Protocol R, **384** (0.14 g, 0.39 mmol), $NaHCO_3$ (0.16 g, 2.0 mmol) and Cbz-Cl (70 μL, 0.47 mmol) in EtOAc/H_2O (1:1, 4.0 mL) afforded (+)-**365** (0.13 g, 96%) as a colorless solid: $[\alpha]_D$ +50.1 (*c* 0.83, $CHCl_3$).



366

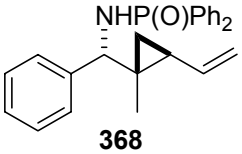
Cbz-*DL*-H$_2$ΔPhg-NHPr^i (366). To a solution of **365** (19 mg, 0.056 mmol) in dry Et_2O (0.50 mL) was added KOTMS (14 mg, 0.11 mmol). The reaction mixture was stirred for 1.5 h, diluted with water, acidified with 10 % HCl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was dissolved in dry CH_2Cl_2 (0.50 mL) and treated with EDCI (14 mg, 0.073 mmol), DMAP (1.0 mg, 8.2 μmol), DIPEA (49 μL, 0.28 mmol) and *i*-$PrNH_2$•HCl (27 mg, 0.28 mmol). The reaction mixture was stirred for 12 h, diluted with EtOAc and washed with water, 10% HCl and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (3:2, hexanes/EtOAc) to give **366** (15 mg, 75%) as a colorless solid: mp 197.5-200.3 °C (hexanes/EtOAc); IR (KBr) 3323, 3060, 3032, 2968, 2929, 1693, 1637, 1542, 1291, 1263, 1227, 1150 cm^{-1}; ^{1}H NMR δ 7.36-7.29 (m, 10 H), 5.59 (bs, 1 H), 5.39 (bd, *J* = 7.0 Hz, 1 H), 5.12, 5.07 (AB, *J* = 12.1 Hz, 2 H), 4.17 (t, *J* = 8.7 Hz, 1 H), 4.06 (octet, *J* = 6.7 Hz, 1 H), 1.85-1.76 (m, 1 H), 1.35-1.19 (m, 2 H), 1.14 (d, *J* = 6.5 Hz, 6 H), 0.76 (ddd, *J* = 8.3, 5.9, 4.6 Hz, 1 H); ^{13}C NMR δ 171.08, 155.90, 140.93, 136.36, 128.69, 128.52, 128.16, 128.00, 127.73, 126.66, 66.80, 58.33, 41.53, 25.89, 22.82, 22.05,

12.36; MS (ESI) *m/z* (intensity) 389 ([M+Na]$^+$, 100); HRMS (ESI) *m/z* calculated for $C_{22}H_{26}N_2O_3Na$ (M+Na) 389.1865, found 389.1857.



367

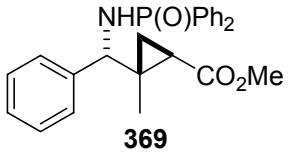
***N*-((*R**)-((1*R**,2*S**)-2-(2-Hydroxyethyl)-1-methylcyclopropyl)(phenyl)methyl)-P,P-diphenylphosphinamide (367)**. According to the General Protocol N, **179** (1.8 g, 2.8 mmol), AcOH (0.32 mL, 5.5 mmol) and TBAF (5.5 mL, 5.5 mmol, 1.0 M in THF) in dry THF (30 mL) afforded **367** (1.1 g, 96%) as a colorless foam: IR (KBr) 3307, 3167, 3077, 3056, 2979, 2960, 2862, 1451, 1438, 1184, 1122 cm^{-1}; ^{1}H NMR δ 7.98-7.91 (m, 2 H), 7.79-7.72 (m, 2 H), 7.55-7.29 (m, 11 H), 3.83-3.65 (m, 3 H), 3.37 (t, *J* = 11.4 Hz, 1 H), 2.08-1.98 (m, 1 H), 1.41-1.31 (m, 1 H), 1.23-1.12 (m, 1 H), 0.95 (s, 3 H), 0.84 (dd, *J* = 9.1, 4.8 Hz, 1 H), 0.15 (t, *J* = 5.4 Hz, 1 H); ^{13}C NMR δ 141.96, 141.85, 133.98, 132.86, 132.73, 132.26, 132.01, 131.98, 131.85, 131.32, 129.54, 128.74, 128.58, 128.41, 128.26, 127.00, 126.50, 64.90, 61.99, 33.27, 26.59, 22.25, 20.25, 12.46; MS (ESI) *m/z* (intensity) 833 ([2M+Na]$^+$, 53), 428 ([M+Na]$^+$, 100); HRMS (ESI) *m/z* calculated for $C_{25}H_{28}NO_2PNa$ (M+Na) 428.1755, found 428.1758.



368

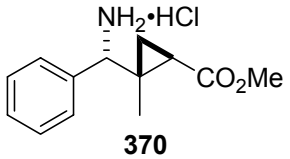
N-((*R)-((1*R**,2*S**)-1-Methyl-2-vinylcyclopropyl)(phenyl)methyl)-*P*,*P*-diphenylphosphinamide (368)**. According to the General Protocol O, **367** (1.1 g, 2.7 mmol), *o*-$NO_2C_6H_4SeCN$ (1.2 g, 5.3 mmol) and Bu_3P (1.1 g, 5.3 mmol) in dry THF (50 mL) followed by Na_2HPO_4 (1.9 g, 13 mmol), *m*-CPBA (1.6 g, 13 mmol, ~70 wt % *m*-CPBA) and *i*-Pr_2NH (1.9 mL, 13 mmol) in dry CH_2Cl_2 (50 mL) afforded **368** (0.85 g, 82%) as a colorless solid: mp 166.7-168.5 °C (hexanes/EtOAc); IR (KBr) 3179, 3058, 2994, 2968, 1634, 1452, 1436, 1184, 1177, 1124, 1106 cm^{-1}; ^{1}H NMR δ 7.91-7.84 (m, 2 H), 7.78-7.71 (m, 2 H), 7.53-7.41 (m, 4 H), 7.35 (m, 7 H), 5.62 (ddd, *J* = 17.1, 10.2, 8.1 Hz, 1 H), 5.15 (ddd, *J* = 17.0, 2.0, 0.8 Hz, 1 H), 5.04 (ddd, *J* = 10.2, 2.0, 0.6 Hz, 1 H), 3.85 (t, *J* = 10.4 Hz, 1 H), 3.35 (dd, *J* = 9.9, 7.1 Hz, 1 H), 1.64 (dt, *J* = 8.3, 5.7 Hz, 1 H), 1.13 (dd, *J* = 8.8, 5.0 Hz, 1 H), 1.01 (s, 3 H), 0.50 (t, *J* = 5.4 Hz, 1 H); ^{13}C NMR δ 142.01, 141.95, 137.46, 137.42, 134.26, 134.17, 133.15, 133.04, 132.52, 132.40, 132.00,

131.88, 131.79, 131.74, 131.68, 131.44, 128.56, 128.54, 128.37, 128.32, 128.17, 127.17, 127.01, 115.24, 62.20, 27.73, 27.68, 26.66, 18.98, 14.92; MS (EI) *m/z* (intensity) 387 (M^+, 17), 346 (20), 333 (28), 306 (3), 270 (37), 218 (55), 201 (100), 186 (40), 170 (40), 155 (42), 132 (62); HRMS (EI) *m/z* calculated for $C_{25}H_{26}NOP$ 387.1752, found 387.1756.



369

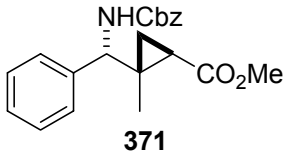
(1*R,2*R**)-Methyl 2-((*R**)-(diphenylphosphinoylamino)(phenyl)methyl)-2-methylcyclopropanecarboxylate (Dpp-$^{\beta}$MeΔPhg-OMe) (369)**. According to the General Protocol P, **368** (0.50 g, 1.3 mmol) in dry CH_2Cl_2 (35 mL) and NaOH (9.0 mL, 2.5M in MeOH) was treated with a stream of O_3 (~4.5% v/v O_3 in O_2) to afford **369** as a colorless solid which was used in the subsequent step without further purification. An analytical sample was purified by recrystallization (hexanes/EtOAc): mp 220.0-222.3 °C (hexanes/EtOAc); IR (KBr) 3203, 3061, 2450, 2878, 1722, 1456, 1437, 1177, 1125, 1109 cm^{-1}; ^1H NMR δ 7.83 (dd, *J* = 11.9, 7.1 Hz, 2 H), 7.73 (dd, *J* = 12.0, 7.4 Hz, 2 H), 7.53-7.43 (m, 4 H), 7.36-7.23 (m, 7 H), 3.92 (t, *J* = 10.6 Hz, 1 H), 3.69 (s, 3 H), 3.38 (t, *J* = 8.8 Hz, 1 H), 1.99 (dd, *J* = 8.4, 5.9 Hz, 1 H), 1.41 (dd, *J* = 8.3, 4.9 Hz, 1 H), 1.16-1.11 (m, 1 H), 1.11 (s, 3 H); ^{13}C NMR δ 172.74, 141.28, 141.22, 133.60, 132.56, 132.43, 131.87, 131.74, 130.88, 128.57, 128.39, 128.19, 127.37, 127.04, 61.21, 51.70, 31.06, 31.00, 24.52, 19.14, 13.80; MS (ESI) *m/z* (intensity) 861 ($[2M+Na]^+$, 60), 442 ($[M+Na]^+$, 100); HRMS (ESI) *m/z* calculated for $C_{25}H_{26}NO_3PNa$ (M+Na) 442.1548, found 442.1563.



370

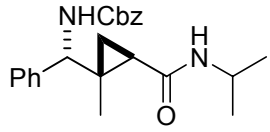
(1*R,2*R**)-Methyl 2-((*R**)-amino(phenyl)methyl)-2-methylcyclopropanecarboxylate hydrochloride ($^{\beta}$MeΔPhg-OMe•HCl) (370)**. According to the General Protocol Q, **369** (0.54 g, 1.3 mmol) and HCl (10 mL, 1.0 M in MeOH) afforded **370** (0.25 g, 75% (2 steps)) as a colorless solid: mp 226.2-228.8 °C (dec., Et_2O/MeOH); IR (KBr) 3430, 2952, 1724, 1596, 1517, 1442, 1196, 1176 cm^{-1}; ^1H NMR (CD_3OD) δ 7.51-7.38 (m, 5 H), 4.01 (s, 1 H), 3.71 (s, 3 H), 2.02 (dd, *J* = 8.7, 5.9 Hz, 1 H), 1.41 (dd, *J* = 8.8, 5.3 Hz, 1 H), 1.19 (s, 3 H), 1.12 (t, *J* = 5.7 Hz, 1 H); ^{13}C

NMR (CD_3OD) δ 173.04, 136.09, 130.12, 130.05, 128.08, 63.30, 52.43, 29.26, 26.61, 19.89, 12.40.



371

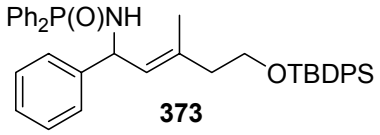
Cbz-$^{\beta}$MeΔPhg-OMe•HCl (371). According to the General Protocol R, **370** (75 mg, 0.29 mmol), $NaHCO_3$ (0.12 g, 1.5 mmol) and Cbz-Cl (50 mL, 0.35 mmol) in EtOAc/H_2O (1:1, 3.0 mL) afforded **370** (86 mg, 83%) as a colorless oil: IR (neat) 3342, 3064, 3032, 3005, 2952, 1716, 1531, 1497, 1441, 1241, 1197, 1174 cm^{-1}; ^1H NMR δ 7.39-7.28 (m, 10 H), 5.27 (bd, *J* = 8.3 Hz, 1 H), 5.14, 5.10 (AB, *J* = 12.2 Hz, 2 H), 4.50 (d, *J* = 6.4 Hz, 1 H), 3.70 (s, 3 H), 1.94 (bm, 1 H), 1.28-1.17 (m, 2 H), 1.11 (s, 3 H); ^{13}C NMR δ 172.39, 155.94, 139.53, 136.31, 128.59, 128.51, 128.16, 128.07, 127.64, 126.82, 67.05, 61.35, 51.69, 29.61, 24.21, 18.95, 13.60; MS (EI) *m/z* (intensity) 262 ($[M-C_7H_7]^+$, 20), 91 (100); HRMS (EI) *m/z* calculated for $C_{21}H_{23}NO_4$ 353.1627, found 353.1623.



372

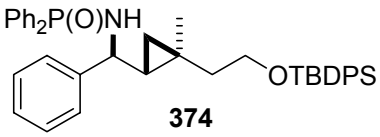
Cbz-(+/-)-$^{\beta}$MeΔPhg-NHPr^{i} (372). **General Protocol S**. To a solution of **371** (30 mg, 0.085 mmol) in MeOH (1.0 mL) was added NaOH (1.0 mL, 2.0 M in H_2O) and THF (0.20 mL). The reaction mixture was stirred for 3 h, acidified with 10% HCl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was dissolved in dry DMF (1.0 mL) and treated at 0 °C with BOP (56 mg, 0.13 mmol), *i*-$PrNH_2$•HCl (41 mg, 0.42 mmol) and DIPEA (74 μL, 0.42 mmol). The mixture was stirred for 30 min, warmed to r.t. and stirred for 4 h, diluted with EtOAc and washed with 10% HCl, H_2O and brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on SiO_2 (3:2, hexanes/EtOAc) to afford **372** (27 mg, 84%) as a colorless solid: mp 149.5-152.1 °C (hexanes/EtOAc); IR (KBr) 3333, 3301, 3063, 3033, 2971, 2943, 1709, 1644, 1544, 1454, 1252 cm^{-1}; ^1H NMR δ 7.39-7.30 (m, 10 H), 5.79 (bs, 1 H), 5.36 (d, *J* = 7.1 Hz, 1 H), 5.16, 5.13 (AB, *J* = 12.6 Hz, 2 H), 4.21 (d, *J* = 7.6 Hz, 1 H), 4.06 (octet, *J* = 6.6 Hz, 1 H), 1.86-1.80 (m, 1 H), 1.19 (t, *J* = 5.4 Hz, 1 H), 1.15 (d, *J* = 6.5 Hz, 3 H), 1.10 (d, *J* = 7.4 Hz, 3 H), 1.09 (s, 3 H), 1.02-0.97

(m, 1 H); ^{13}C NMR δ 169.33, 156.17, 139.24, 136.28, 128.60, 128.27, 127.96, 127.65, 126.79, 66.92, 62.92, 41.41, 28.90, 27.03, 23.06, 22.74, 16.41, 12.17; MS (ESI) *m/z* (intensity) 403 ([M+Na]$^+$, 100); HRMS (ESI) *m/z* calculated for $C_{23}H_{28}N_2O_3Na$ (M+Na) 403.1998, found 403.2009.



373

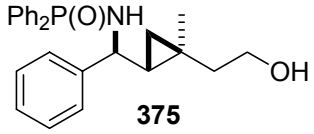
N*-((*E*)-5-(*tert*-Butyldiphenylsilyloxy)-3-methyl-1-phenylpent-2-enyl)-*P*,*P*-diphenylphosphinamide (373)**. To a solution of Cp_2ZrCl_2 (0.77 g, 2.6 mmol) in dry CH_2Cl_2 (50 mL) was added a freshly prepared solution of Me_3Al (3.8 g, 52 mmol) in dry CH_2Cl_2 (10 mL). The light yellow reaction mixture was cooled to 0 °C, treated dropwise with H_2O (0.47 mL, 26 mmol) (Caution: exothermic***), warmed to r.t., stirred for 10 min, cooled to 0 °C and treated dropwise with a solution of **125** (8.1 g, 26 mmol) in dry CH_2Cl_2 (20 mL). The solution was stirred for 40 min and distributed equally via syringe to 16 10 mL microwave tubes containing **21** (0.25 g, 0.82 mmol). The microwave tubes were heated in the microwave reactor for 7.5 min (100 °C, 300W) then poured into an ice/sat. $NaHCO_3$ mixture and filtered through Celite. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (2:3 then 1:4, then 0:1 hexanes/EtOAc) to give **373** (7.0 g, 85%) as a colorless foam: IR (neat) 3241, 3070, 2930, 2857, 1438, 1428, 1184, 1111 cm^{-1}; ^{1}H NMR δ 7.96-7.81 (m, 4 H), 7.67-7.63 (m, 4 H), 7.45-7.30 (m, 14 H), 7.29-7.16 (m, 3 H), 5.40 (d, *J* = 9.3 Hz, 1 H), 5.08 (app. q, *J* = 9.1 Hz, 1 H), 3.64 (t, *J* = 6.7 Hz, 2 H), 3.41 (bm, 1 H), 2.32-2.10 (m, 2 H), 1.36 (d, *J* = 1.0 Hz, 3 H), 1.01 (s, 9 H); ^{13}C NMR δ 135.56, 134.57, 133.97, 132.64, 132.51, 132.10, 131.98, 131.85, 129.54, 128.68, 128.53, 128.38, 128.30, 128.21, 127.60, 127.07, 126.92, 62.55, 53.11, 42.48, 26.84, 19.12, 16.58; MS (EI) *m/z* (intensity) 629 (M$^+$, 1), 572 (44), 416 (15), 355 (65), 216 (31), 199 (100); HRMS (EI) *m/z* calculated for $C_{40}H_{44}NO_2SiP$ 629.2879, found 629.2889.



374

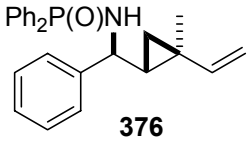
***N*-(*S**)-(((1*R**,2*S**)-2-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-2-methylcyclopropyl)(phenyl)-methyl)-*P*,*P*-diphenylphosphinamide (374)**. To a freshly prepared solution of Et_2Zn (13 g,

0.10 mol) in dry CH_2Cl_2 (65 mL) was added dry DME (11 mL, 0.10 mol). The reaction mixture was cooled to -20 °C, treated dropwise with CH_2I_2 (17 mL, 0.21 mol), stirred for 10 min and treated with a solution of **373** (6.6 g, 10 mmol) in dry CH_2Cl_2 (40 mL). The solution was stirred for 48 h, quenched with sat. NH_4Cl and extracted with CH_2Cl_2 (2x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (2:3 then 1:4, then 0:1 hexanes/EtOAc) to give **374** (6.4 g, 95%) as a colorless foam: IR (neat) 3183, 3056, 2930, 2857, 1438, 1428, 1188, 1110 cm^{-1}; ^1H NMR δ 7.97-7.90 (m, 2 H), 7.79-7.73 (m, 2 H), 7.62-7.57 (m, 4 H), 7.48-7.31 (m, 13 H), 7.23-7.19 (m, 4 H), 3.80 (t, *J* = 10.0 Hz, 1 H), 3.56-3.41 (m, 2 H), 3.29 (bs, 1 H), 1.55-1.45 (m, 1 H), 1.40-1.28 (m, 1 H), 1.04-0.94 (m, 1 H), 1.00 (s, 9 H), 0.80 (s, 3 H), 0.56 (dd, *J* = 8.5, 5.0 Hz, 1 H), 0.35 (t, *J* = 5.2 Hz, 1 H); ^{13}C NMR δ 144.40, 144.32, 135.49, 134.03, 133.94, 132.28, 132.22, 132.15, 132.10, 131.68, 131.57, 131.54, 129.47, 128.39, 128.30, 128.21, 128.14, 127.53, 126.98, 126.66, 62.23, 56.66, 43.46, 31.64, 31.58, 26.82, 19.95, 19.60, 19.04, 18.27; MS (EI) *m/z* (intensity) 643 (M^+, 2), 586 (97), 508 (16), 369 (35), 319 (40), 306 (100), 218 (32), 201 (84), 183 (26), 135 (29); HRMS (EI) *m/z* calculated for $C_{41}H_{46}NO_2SiP$ 643.3035, found 643.3035.



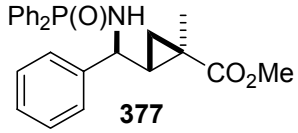
375

***N*-(*S**)-(((1*R**,2*S**)-2-(2-Hydroxyethyl)-2-methylcyclopropyl)(phenyl)methyl)-*P*,*P*-diphenylphosphinamide 375**. According to the General Protocol N, **374** (6.4 g, 9.9 mmol), AcOH (1.1 mL, 20 mmol) and TBAF (20 mL, 20 mmol, 1.0 M in THF) in dry THF (50 mL) afforded **375** (3.6 g, 91%) as a colorless foam: IR (neat) 3237, 3058, 2928, 1438, 1188 cm^{-1}; ^1H NMR δ 7.96-7.90 (m, 2 H), 7.78-7.71 (m, 2 H), 7.53-7.39 (m, 4 H), 7.45-7.24 (m, 7 H), 3.87 (bt, *J* = 9.4 Hz, 1 H), 3.49-3.39 (m, 3 H), 1.59-1.50 (m, 2 H), 1.18-1.10 (m, 1 H), 0.93 (s, 3 H), 0.55 (dd, *J* = 8.3, 4.9 Hz, 1 H), 0.46 (t, *J* = 5.3 Hz, 1 H); ^{13}C NMR δ 144.28, 144.21, 132.14, 132.01, 131.98, 131.85, 131.56, 131.43, 128.38, 128.25, 128.14, 128.08, 127.98, 127.00, 126.45, 60.12, 56.59, 43.25, 31.67, 31.61, 19.35, 19.01, 17.88; MS (EI) *m/z* (intensity) 405 (M^+, 1), 374 (4), 306 (31), 216 (40), 201 (59), 149 (41), 59 (100); HRMS (EI) *m/z* calculated for $C_{25}H_{28}NO_2P$ 405.1858, found 405.1859.



376

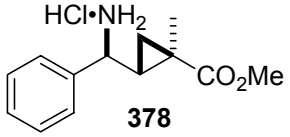
***N*-(*S**)-(((1*R**,2*S**)-2-Methyl-2-vinylcyclopropyl)(phenyl)methyl)-*P*,*P*-diphenylphosphinamide (376)**. According to the General Protocol O, **375** (3.5 g, 8.6 mmol), *o*-$NO_2C_6H_4SeCN$ (3.9 g, 17 mmol) and Bu_3P (3.5 g, 17 mmol) in dry THF (0.15 L) followed by Na_2HPO_4 (6.1 g, 43 mmol), *m*-CPBA (5.1 g, 21 mmol, ~70% w/w *m*-CPBA) and *i*-Pr_2NH (6.0 mL, 43 mmol) in dry CH_2Cl_2 (0.15 L) afforded crude **376**. The residue was purified by chromatography on deactivated SiO_2 (9:1 then 4:1 CH_2Cl_2/acetone containing 1% v/v Et_3N) to afford a yellow/orange solid which was re-purified by chromatography on deactivated SiO_2 (2:3, then 25:75 then 1:4 hexanes/EtOAc containing 1% v/v Et_3N) to afford **376** (2.7 g, 81%) as a colorless solid: mp 190.6-192.2 °C (hexanes/EtOAc); IR (KBr) 3259, 3058, 3002, 2975, 2944, 1630, 1438, 1185, 1123 cm^{-1}; ^1H NMR δ 8.00-7.94 (m, 2 H), 7.87-7.80 (m, 2 H), 7.54-7.22 (m, 11 H), 5.39 (dd, *J* = 16.8, 11.0 Hz, 1 H), 4.85-4.79 (m, 2 H), 3.96 (app q, *J* = 8.7 Hz, 1 H), 3.35-3.25 (m, 1 H), 1.31 (dt, *J* = 9.5, 6.1 Hz, 1 H), 0.94 (s, 3 H), 0.86 (dd, *J* = 8.6, 5.1 Hz, 1 H), 0.63 (t, *J* = 5.7 Hz, 1 H); ^{13}C NMR δ 145.97, 143.93, 143.85, 132.32, 132.20, 132.08, 131.75, 131.71, 131.68, 128.47, 128.44, 128.40, 128.27, 128.23, 127.14, 126.92, 109.92, 56.20, 32.75, 32.70, 23.98, 21.33, 15.94; MS (EI) *m/z* (intensity) 387 (M^+, 28), 319 (80), 396 (41), 218 (35), 201 (100); HRMS (EI) *m/z* calculated for $C_{25}H_{26}NOP$ 387.1752, found 387.1751.



377

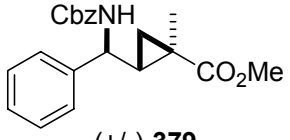
(1*R,2*R**)-Methyl 2-((*S**)-(diphenylphosphinoylamino)(phenyl)methyl)-1-methylcyclopropanecarboxylate (Dpp-$^{\alpha}$MeΔPhg-OMe) (377)**. According to the General Protocol P, **376** (2.6 g, 6.7 mmol) and NaOH (50 mL, 2.5 M in MeOH) in dry CH_2Cl_2 (0.20 L) was treated with O_3 (~4.5% v/v O_3 in O_2) to afford **377** (2.8 g, 98%) as a colorless foam that was used in the next reaction without further purification. An analytical sample was purified by chromatography on deactivated SiO_2 (1:9, hexanes/EtOAc containing 1% v/v Et_3N) to afford a colorless foam: IR (neat) 3181, 1720, 1438, 1192, 1123, 1110 cm^{-1}; ^1H NMR δ 7.97-7.90 (m, 2 H), 7.80-7.73 (m, 2 H), 7.51-7.42 (m, 4 H), 7.38-7.24 (m, 7 H), 3.92 (app q, *J* = 9.8 Hz, 1 H), 3.58 (s, 3 H), 3.47 (bt, *J* = 7.5 Hz, 1 H), 2.04 (dt, *J* = 9.3, 6.7 Hz, 1 H), 1.36 (dd, *J* = 9.1, 4.6 Hz, 1 H), 1.08 (s, 3 H),

0.76 (dd, *J* = 6.6, 4.6 Hz, 1 H); ^{13}C NMR δ 175.48, 143.26, 143.19, 134.02, 133.19, 132.31, 132.19, 132.06, 131.84, 131.80, 131.75, 131.72, 131.49, 128.66, 128.45, 128.41, 128.28, 128.24, 127.39, 126.71, 55.57, 51.92, 33.17, 33.11, 24.52, 22.86, 14.30; MS (ESI) *m/z* (intensity) 861 ([2M+Na]$^+$, 95), 442 ([M+Na]$^+$, 100), 420 ([M+H]$^+$, 29); HRMS (EI) *m/z* calculated for $C_{25}H_{26}NO_3PNa$ (M+Na) 442.1548, found 442.1569.



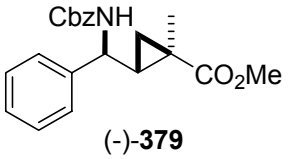
378

(1*R,2*R**)-Methyl 2-((*S**)-amino(phenyl)methyl)-1-methylcyclopropanecarboxylate hydrochloride ($^{\alpha}$MeΔPhg-OMe•HCl) (378)**. According to the General Protocol Q, **377** (2.7 g, 6.6 mmol) in HCl (50 mL, 2.0 M in MeOH) afforded **378** (1.3 g, 80%) as a colorless solid: mp 279.8-281.2 °C (dec., Et_2O/MeOH); IR (KBr) 3437, 3026, 2903, 1721, 1597, 1512, 1499, 1458, 1438, 1200, 1166 cm^{-1}; ^{1}H NMR (MeOD) δ 7.51-7.42 (m, 5 H), 4.11 (d, *J* = 11.0 Hz, 1 H), 3.63 (s, 3 H), 2.18 (ddd, *J* = 11.0, 8.8, 6.4 Hz, 1 H), 1.58 (dd, *J* = 8.8, 4.6 Hz, 1 H), 1.23 (s, 3 H), 1.06 (dd, *J* = 6.4, 4.7 Hz, 1 H); ^{13}C NMR δ 176.15, 137.98, 130.58, 130.48, 128.36, 57.10, 52.88, 29.36, 24.80, 22.06, 14.35.



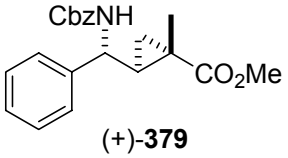
(+/-)-**379**

Cbz-(+/-)-$^{\alpha}$MeΔPhg-OMe ((+/-)-379). According to the General Protocol R, **378** (1.2 g, 4.9 mmol), $NaHCO_3$ (2.0 g, 24 mmol) and Cbz-Cl (0.84 mL, 5.9 mmol) in EtOAc/H_2O (1:1, 50 mL) afforded (+/-)-**379** (1.7 g, 97%) as a colorless oil which solidified on standing: IR (neat) 3343, 3064, 3032, 2952, 1719, 1526, 1455, 1284, 1257, 1199, 1166 cm^{-1}; ^{1}H NMR δ 7.36-7.28 (m, 10 H), 5.24 (bd, *J* = 6.4 Hz, 1 H), 5.12, 5.11 (AB, *J* = 12.3 Hz, 2 H), 4.50 (bt, *J* = 9.2 Hz, 1 H), 3.65 (s, 3 H), 1.96 (dt, *J* = 9.2, 7.0 Hz, 1 H), 1.47 (dd, *J* = 9.1, 4.3 Hz, 1 H), 1.33 (s, 3 H), 0.97-0.91 (m, 1 H); ^{13}C NMR δ 175.50, 155.87, 141.62, 136.39, 128.78, 128.52, 128.14, 128.05, 127.65, 126.51, 66.94, 55.03, 52.10, 31.44, 23.82, 21.30, 14.40; MS (EI) *m/z* (intensity) 353 (M$^+$, 2), 253 (16), 209 (12), 176 (7), 143 (8), 113 (12), 91 (100); HRMS (EI) *m/z* calculated for $C_{21}H_{23}NO_4$ 353.1627, found 353.1626.



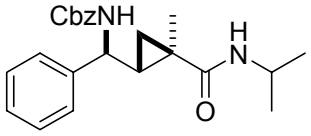
(-)-**379**

Cbz-*D*-$^{\alpha}$MeΔPhg-OMe ((-)-379). According to the General Protocol R, **385** (0.30 g, 0.81 mmol), $NaHCO_3$ (0.34 g, 4.1 mmol) and Cbz-Cl (0.14 mL, 0.98 mmol) in EtOAc/H_2O (1:1, 8.0 mL) afforded (-)-**379** (0.29 g, 100%) as a colorless solid: $[\alpha]_D$ -57.3 (*c* 1.2, $CHCl_3$).



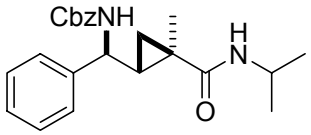
(+)-**379**

Cbz-*L*-$^{\alpha}$MeΔPhg-OMe ((+)-379). According to the General Protocol R, **386** (0.25 g, 0.68 mmol), $NaHCO_3$ (0.28 g, 3.4 mmol) and Cbz-Cl (0.12 mL, 0.81 mmol) in EtOAc/H_2O (1:1, 6.0 mL) afforded (+)-**379** (0.22 g, 94%) as a colorless solid: $[\alpha]_D$ +58.3 (*c* 0.65, $CHCl_3$).



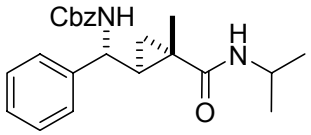
(+/-)-**380**

Cbz-*DL*-$^{\alpha}$MeΔPhg-NHPr^{i} ((+/-)-380). According to the General Protocol S, (+/-)-**379** (20 mg, 0.057 mmol) and NaOH (1.0 mL, 2.0 M in H_2O) in MeOH (1.0 mL) and THF (0.20 mL) followed by *i*-$PrNH_2$•HCl (16 mg, 0.17 mmol), BOP (38 mg, 0.085 mmol) and DIPEA (44 μL, 0.26 mmol) in dry DMF (0.50 mL) {Reaction time for coupling = 10 h} afforded, after purification by chromatography on deactivated SiO_2 (3:2, hexanes/EtOAc containing 1% v/v Et_3N), (+/-)-**380** (20 mg, 94%) as a colorless solid: mp 129.0-131.5 °C (hexanes/EtOAc); IR (KBr) 3372, 3264, 3032, 2973, 1700, 1634, 1530, 1455, 1281, 1258, 1213 cm^{-1}; ^{1}H NMR δ 7.36-7.28 (m, 10 H), 5.49-5.43 (m, 2 H), 5.11, 5.10 (AB, *J* = 12.3 Hz, 2 H), 4.49 (bt, *J* = 9.1 Hz, 1 H), 4.05 (octet, *J* = 6.6 Hz, 1 H), 2.00-1.92 (m, 1 H), 1.48 (dd, *J* = 9.1, 4.1 Hz, 1 H), 1.27 (s, 3 H), 1.11 (d, *J* = 6.5 Hz, 3 H), 1.10 (d, *J* = 6.5 Hz, 3 H), 0.85-0.78 (m, 1 H); ^{13}C NMR δ 173.10, 155.99, 142.05, 136.46, 128.64, 128.48, 128.07, 128.01, 127.51, 126.69, 66.84, 55.11, 41.66, 30.19, 24.01, 22.77, 22.72, 20.24, 14.82; MS (ESI) *m/z* (intensity) 403 ($[M+Na]^+$, 100); HRMS (ESI) *m/z* calculated for $C_{23}H_{28}N_2O_3Na$ (M+Na) 403.1998, found 403.2007.



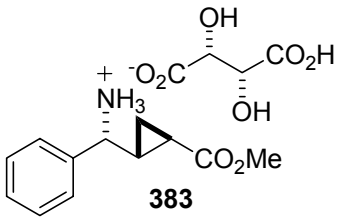
(-)-**380**

Cbz-*D*-$^{\alpha}$MeΔPhg-NHPr^{i} prepared from (-)-**379 (**(-)-**380)**. According to the General Protocol S, (-)-**379** (10 mg, 27 μmol), BOP (18 mg, 41 μmol), *i*-PrNH$_2$•HCl (13 mg, 0.14 mmol), and DIPEA (28 μL, 0.16 mmol) in dry DMF (0.50 mL) afforded (-)-**380** (8.4 mg, 82%) as a colorless solid: $[\alpha]_D$ -53.5 (*c* 0.40, $CHCl_3$).

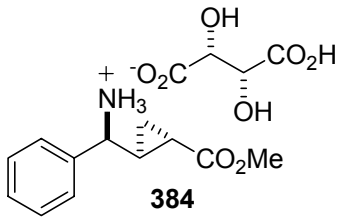


(+)-**380**

Cbz-*L*-$^{\alpha}$MeΔPhg-NHPr^{i} prepared from (+)-**379 (**(+)-**380)**. According to the General Protocol S, (+)-**379** (10 mg, 27 μmol), BOP (18 mg, 41 μmol), *i*-PrNH$_2$•HCl (13 mg, 0.14 mmol), and DIPEA (28 μL, 0.16 mmol) in dry DMF (0.50 mL) afforded (+)-**380** (9.7 mg, 94%) as a colorless solid: $[\alpha]_D$ +52.1 (*c* 0.47, $CHCl_3$).



383

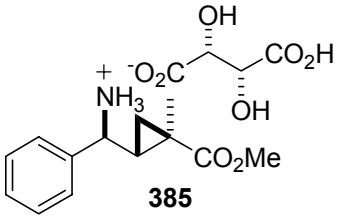


384

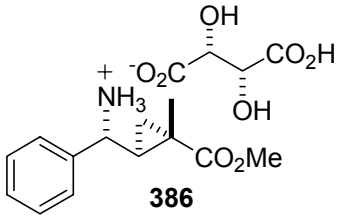
(1*R*,2*R*)-Methyl 2-((*R*)-amino(phenyl)methyl)cyclopropanecarboxylate *L*-tartaric acid salt (383) and (1*S*,2*S*)-Methyl 2-((*S*)-amino(phenyl)methyl)cyclopropanecarboxylate *L*-tartaric acid salt (384). **General Protocol T**. To a mixture of (+/-)-**365** (1.3 g, 3.9 mmol) and Pd/C (0.41 g, 0.39 mmol) was added under N_2 MeOH (30 mL). The flask was evacuated and purged with H_2 (1 atm), and the reaction mixture was vigorously stirred for 2 h, filtered through Celite and concentrated to afford a colorless oil. The residue was dissolved in EtOH, treated with *L*-tartaric acid (0.59 g, 3.9 mmol) and H_2O, and heated until all solid material was dissolved and concentrated to dryness. The resultant colorless solid was suspended in EtOH and heated at reflux. A minimal amount of H_2O was added until all solid material dissolved. The solution was allowed to stand for 48 h during which time **383** slowly crystallized from the solution. The mixture was filtered and the filter cake was recrystallized from EtOH/H_2O until the optical

rotation was constant affording **383** (0.76 g, 40%) as a colorless solid. The filtrate from the first crystallization was concentrated, dissolved in EtOH and heated at reflux. Dry Et_2O was added until a precipitate was observed. Sufficient EtOH was added to dissolve all solid material and the solution was cooled to r.t. and allowed to stand for 24 h. The colorless solid was filtered and recrystallized from EtOH/Et_2O to afford **384** (0.70 g, 37%) as a colorless solid. **383**: mp 199.5-201.7 °C (EtOH/H_2O); $[\alpha]_D$ -26.4 (*c* 0.57, H_2O); IR (KBr) 3488, 3321, 3271, 2961, 2903, 1887, 1712, 1595, 1503, 1412, 1304, 1237, 1176, 1135 cm^{-1}; ^1H NMR (MeOD) δ 7.47-7.41 (m, 5 H), 4.38 (s, 2 H), 3.84-3.80 (m, 1 H), 3.70 (s, 3 H), 2.05-1.95 (m, 2 H), 1.19 (dt, *J* = 8.6, 5.2 Hz, 1 H), 1.03 (ddd, *J* = 8.3, 6.6, 4.7 Hz, 1 H); ^{13}C NMR δ 176.95, 174.70, 137.70, 130.36, 128.19, 74.14, 59.11, 52.57, 26.03, 21.06, 13.86.

384: mp 174.2-176.4°C (EtOH/Et_2O); $[\alpha]_D$ +46.0 (*c* 0.51, H_2O); IR (KBr) 3320, 3273, 2960, 1875, 1713, 1595, 1412, 1304, 1216, 1175, 1135 cm^{-1}; ^1H NMR (MeOD) δ 7.50-7.40 (m 5 H), 4.40 (s, 2 H), 3.84 (d, *J* = 9.3 Hz, 1 H), 3.69 (s, 3 H), 2.06-1.97 (m, 2 H), 1.21-1.14 (m, 1 H), 1.06-1.00 (m, 1 H); ^{13}C NMR δ 177.06, 174.79, 137.72, 130.29, 128.25, 74.17, 59.02, 52.58, 26.03, 21.04, 13.89.



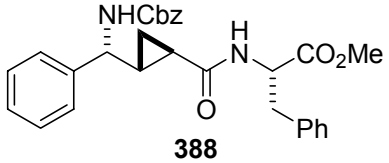
385



386

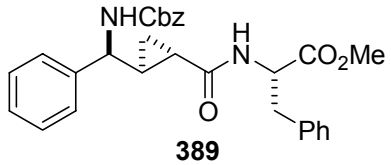
(1*R*,2*R*)-Methyl 2-((*S*)-amino(phenyl)methyl)-1-methylcyclopropanecarboxylate *L*-tartaric acid salt (385) and (1*S*,2*S*)-Methyl 2-((*R*)-amino(phenyl)methyl)-1-methylcyclopropane-carboxylate *L*-tartaric acid salt (386). According to the General Protocol T, (+/-)-**379** (1.6 g, 4.6 mmol), Pd/C (0.48 g, 0.46 mmol), and *L*-tartaric acid (0.68 g, 4.6 mmol) afforded **385** (0.63 g, 38%) and **386** (0.55 g, 32%) as colorless solids. **385**: mp 172.1-174.1 °C (EtOH/H_2O); $[\alpha]_D$ -22.3 (*c* 0.45, H_2O); IR (KBr) 3322, 3272, 3029, 2975, 2912, 1728, 1698, 1589, 1499, 1412, 1305, 1264, 1214 cm^{-1}; ^1H NMR (MeOD) δ 7.50-7.39 (m, 5 H), 4.39 (s, 2 H), 4.09 (d, *J* = 11.0 Hz, 1 H), 3.62 (s, 3 H), 2.17 (ddd, *J* = 10.9, 8.8, 6.5 Hz, 1 H), 1.57 (dd, *J* = 8.9, 4.6 Hz, 1 H), 1.22 (s, 3 H), 1.07 (dd, *J* = 6.3, 4.8 Hz, 1 H); ^{13}C NMR (MeOD) δ 176.99, 176.29, 138.23, 130.46, 130.42, 128.36, 74.16, 56.97, 52.85, 29.51, 24.82, 22.09, 14.35.

386: mp 194.2-196.0 °C (EtOH/Et_2O); $[\alpha]_D$ +52.2 (*c* 0.51, H_2O); IR (KBr) 3439, 3322, 3273, 3028, 2975, 2906, 1729, 1590, 1499, 1412, 1306, 1265, 1215 cm^{-1}; ^1H NMR (MeOD) δ 7.50-7.40 (m, 5 H), 4.39 (s, 2 H), 4.09 (d, *J* = 11.0 Hz, 1 H), 3.62 (s, 3 H), 2.17 (ddd, *J* = 10.9, 8.9, 6.5 Hz, 1 H), 1.57 (dd, *J* = 8.8, 4.6 Hz, 1 H), 1.22 (s, 3 H), 1.07 (dd, *J* = 6.3, 4.7 Hz, 1 H); ^{13}C NMR (MeOD) δ 177.05, 176.30, 138.25, 130.41, 128.38, 74.19, 56.96, 52.84, 29.52, 24.83, 22.11, 14.36.



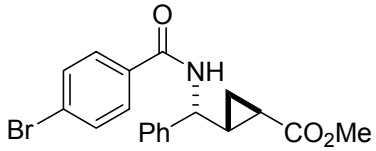
388

Cbz-*L*-H_2ΔPhg-*L*-Phe-OMe (388). **General Protocol U**. To a solution of (-)-**365** (19 mg, 56 μmol) in dry Et_2O (1.0 mL) was added KOTMS (14 mg, 0.11 mmol). The reaction mixture was stirred for 12 h, diluted with H_2O, acidified with 10% HCl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was dissolved in dry CH_2Cl_2 (1.0 mL) and treated with *L*-Phe-OMe•HCl (12 mg, 56 μmol), EDCI (13 mg, 0.067 mmol), DMAP (1.0 mg, 8.2 μmol) and DIPEA (25 μL, 0.14 mmol). The reaction mixture was stirred for 12 h, diluted with H_2O and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude residue was analyzed by HPLC (Microsorb-MV 100 column, 3:1, hexanes/EtOAc, 1.0 mL/min), indicating >99% de (R_t 13.2 min (mixture of **388** and **389**, R_t 10.6, 13.2 min)). The residue was purified by chromatography on deactivated SiO_2 (2:1, hexanes/EtOAc containing 1% v/v Et_3N) to afford **388** (20 mg, 73%) as a colorless solid: mp 166.0-168.4 °C (hexanes/EtOAc); $[\alpha]_D$ +35.2 (*c* 0.4, $CHCl_3$); IR (KBr) 3322, 3031, 2951, 1736, 1688, 1644, 1535, 1248 cm^{-1}; ^1H NMR δ 7.37-7.20 (m, 13 H), 7.12-7.09 (m, 2 H), 6.24 (bd, *J* = 7.3 Hz, 1 H), 5.29 (d, *J* = 7.8 Hz, 1 H), 5.15-5.06 (m, 2 H), 4.95-4.88 (m, 1 H), 4.21 (t, *J* = 8.2 Hz, 1 H), 3.73 (s, 3 H), 3.16, 3.04 (AB of ABX, J_{AB} = 13.8 Hz, J_{AX} = 5.8 Hz, J_{BX} = 6.1 Hz, 2 H), 1.78-1.65 (m, 2 H), 1.27-1.23 (m, 1 H), 0.84-0.77 (m, 1 H); ^{13}C NMR δ 171.95, 171.50, 155.80, 140.85, 136.24, 135.85, 129.29, 128.68, 128.51, 128.17, 128.10, 127.73, 127.04, 126.55, 66.90, 57.97, 53.11, 52.28, 38.03, 26.45, 21.47, 12.58; MS (EI) *m/z* (intensity) 486 (M^+, 2), 91 (100); HRMS (EI) *m/z* calculated for $C_{29}H_{30}N_2O_5$ 486.2154, found 486.2132.



389

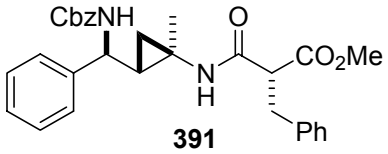
Cbz-*D*-H_2ΔPhg-*L*-Phe-OMe (389). According to the General Protocol U, (+)-**365** (18 mg, 53 μmol) and KOTMS (14 mg, 0.11 mmol) in dry Et_2O (1.0 mL) followed by *L*-Phe-OMe•HCl (13 mg, 58 μmol), EDCI (12 mg, 64 μmol), DMAP (1.0 mg, 8.2 μmol) and DIPEA (24 μL, 0.13 mmol) in dry CH_2Cl_2 (1.0 mL) afforded **389** (19 mg, 75%) as a colorless solid. The crude reaction mixture was analyzed by HPLC (Microsorb-MV 100 column, 3:1, hexanes/EtOAc, 1.0 mL/min), indicating 98.6% de (R_t 10.8 min (mixture of **388** and **389**, R_t 10.6, 13.2 min)): mp 174.7-176.6 °C (hexanes/EtOAc); $[\alpha]_D$ +70.6 (*c* 0.93, $CHCl_3$); IR (KBr) 3321, 3063, 3030, 2951, 1742, 1687, 1638, 1543, 1261, 1219 cm^{-1}; ^1H NMR δ 7.33-7.23 (m, 13 H), 7.12-7.10 (m, 2 H), 6.30 (d, *J* = 7.7 Hz, 1 H), 5.32 (d, *J* = 7.9 Hz, 1 H), 5.06 (s, 2 H), 4.90 (dt, *J* = 7.8, 5.9 Hz, 1 H), 4.21 (bt, *J* = 7.9 Hz, 1 H), 3.72 (s, 3 H), 3.13, 3.10 (AB of ABX, J_{AB} = 13.9 Hz, $J_{AX} = J_{BX}$ = 5.9 Hz, 2 H), 1.84-1.74 (m, 2 H), 1.27-1.22 (m, 1 H), 0.85-0.79 (m, 1 H); ^{13}C NMR δ 172.00, 171.72, 155.91, 140.82, 136.36, 135.92, 129.28, 128.72, 128.54, 128.47, 128.08, 128.04, 127.76, 127.08, 126.65, 66.92, 58.04, 53.35, 52.21, 38.04, 26.25, 21.56, 12.44; MS (EI) *m/z* (intensity) 486 (M^+, 1), 162 (53), 91 (100); HRMS (EI) *m/z* calculated for $C_{29}H_{30}N_2O_5$ 486.2155, found 486.2154.



390

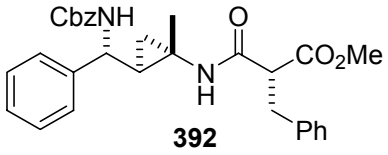
(1*R,2*R**)-Methyl 2-((*R**)-(4-bromobenzamido)(phenyl)methyl)cyclopropanecarboxylate (390)**. To a cooled (0 °C) solution of **383** (26 mg, 0.073 mmol) in dry CH_2Cl_2 (1.0 mL) was added DMAP (1 mg, 8.1 μmol), Et_3N (0.10 mL, 0.72 mmol) and *p*-bromobenzoyl chloride (80 mg, 0.36 mmol). The reaction mixture was warmed to r.t., stirred for 2 h, quenched with sat. $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (7:3, hexanes/EtOAc) to give **390** (20 mg, 70%) as a colorless solid: mp 179.8-181.6 °C (hexanes/EtOAc); $[\alpha]_D$ -58.1 (*c* 0.38, $CHCl_3$); IR (KBr) 3337, 3088, 3027, 2947, 1724, 1635,

1530, 1206, 1183 cm^{-1}; ^1H NMR δ 7.66-7.64 (m, 2 H), 7.59-7.56 (m, 2 H), 7.43-7.30 (m, 5 H), 6.53 (d, *J* = 8.2 Hz, 1 H), 4.79 (t, *J* = 8.4 Hz, 1 H), 3.68 (s, 3 H), 2.02-1.94 (m, 2 H), 1.36-1.30 (m, 1 H), 1.07-1.00 (m, 1 H); ^{13}C NMR δ 174.08, 165.79, 140.45, 133.02, 131.84, 128.88, 128.64, 127.96, 126.75, 126.39, 55.88, 51.93, 26.79, 19.18, 14.22; MS (EI) *m/z* (intensity) 389 (M^+, 2), 387 (M^+, 2), 303 (37), 301 (35), 204 (59), 185 (98), 183 (100), 157 (40), 155 (43), 129 (44), 104 (55); HRMS (EI) *m/z* calculated for $C_{19}H_{18}NO_3Br$ 387.0470, found 387.0467.



391

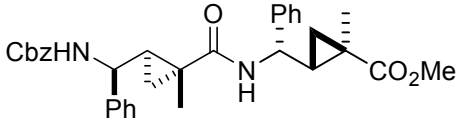
Cbz-*D*-$^{\alpha}$MeΔPhg-*L*-Phe-OMe (391). According to the General Protocol U, (-)-**379** (24 mg, 0.068 mmol) and KOTMS (35 mg, 0.27 mmol) in dry Et_2O (1.0 mL) followed by *L*-Phe-OMe•HCl (23 mg, 0.11 mmol), EDCI (16 mg, 0.085 mmol), DMAP (1.0 mg, 7.1 μmol) and DIPEA (18 μL, 0.11 mmol) in dry CH_2Cl_2 (1.0 mL) afforded **391** (20 mg, 59%) as a colorless solid. The crude reaction mixture was analyzed by HPLC (Microsorb-MV 100 column, 7:3, hexanes/EtOAc, 1.0 mL/min) indicating >99% de (R_t 6.0 min (mixture of **391** and **392**, R_t 4.5, 5.9 min)): mp 94.0-95.5 °C (hexanes/EtOAc); $[\alpha]_D$ +41.1 (*c* 0.95, $CHCl_3$); IR (KBr) 3393, 3367, 3316, 3062, 3031, 3004, 2953, 1742, 1696, 1645, 1525, 1496, 1455, 1435, 1266, 1240, 1211 cm^{-1}; ^1H NMR δ 7.38-7.33 (m, 10 H), 7.21-7.12 (m, 3 H), 6.90 (d, *J* = 6.7 Hz, 2 H), 6.11 (d, *J* = 7.4 Hz, 1 H), 5.33-5.25 (m, 1 H), 5.12, 5.10 (AB, *J* = 12.2 Hz, 2 H), 4.87 (dt, *J* = 7.6, 5.3 Hz, 1 H), 4.47 (bt, *J* = 8.9 Hz, 1 H), 3.73 (s, 3 H), 3.09, 3.07 (AB of ABX, J_{AB} = 13.7 Hz, $J_{AX} = J_{BX}$ = 5.5 Hz, 2 H), 1.98 (dt, *J* = 9.1, 7.7 Hz, 1 H), 1.48 (dd, *J* = 9.1, 4.3 Hz, 1 H), 1.25 (s, 3 H), 0.91-0.82 (m, 1 H); ^{13}C NMR δ 173.50, 171.84, 155.89, 142.02, 136.42, 135.59, 129.14, 128.73, 128.44, 127.98, 127.59, 127.00, 126.64, 66.81, 55.33, 53.18, 52.24, 37.60, 30.76, 23.94, 20.62, 14.35; MS (EI) *m/z* (intensity) 500 (M^+, 74), 260 (20), 91 (100); HRMS (EI) *m/z* calculated for $C_{30}H_{32}N_2O_5$ 500.2311, found 500.2307.



392

Cbz-*L*-$^{\alpha}$MeΔPhg-*L*-Phe-OMe (392). According to the General Protocol S, (+)-**379** (27 mg, 0.076 mmol) and NaOH (0.50 mL, 2.0 M in H_2O) in MeOH (0.50 mL) and THF (0.20 mL)

followed by *L*-Phe-OMe•HCl (25 mg, 0.11 mmol), BOP (40 mg, 0.091 mmol), and DIPEA (33 μL, 0.19 mmol) in dry DMF (1.0 mL) afforded **392** (33 mg, 85%) as a colorless solid. The crude reaction mixture was analyzed by HPLC (Microsorb-MV 100 column, 7:3, hexanes/EtOAc, 1 mL/min) indicating >99% de (R_t 4.6 min (mixture of **391** and **392**, R_t 4.5, 5.9 min)): mp 108.0-110.5 °C (hexanes/EtOAc); $[\alpha]_D$ +73.0 (*c* 0.33, $CHCl_3$); IR (KBr) 3379, 3065, 3031, 2953, 1720, 1700, 1651, 1521, 1455, 1289, 1277, 1256, 1211 cm^{-1}; ^1H NMR δ 7.37-7.20 (m, 13 H), 7.06-7.03 (m, 2 H), 6.07 (d, *J* = 7.6 Hz, 1 H), 5.37 (bd, *J* = 7.7 Hz, 1 H), 5.11, 5.10 (AB, *J* = 12.2 Hz, 2 H), 4.82 (dt, *J* = 5.9, 5.8 Hz, 1 H), 4.48 (bt, *J* = 9.2 Hz, 1 H), 3.69 (s, 3 H), 3.12, 3.06 (AB of ABX, J_{AB} = 13.8 Hz, $J_{AX} = J_{BX}$ = 5.8 Hz, 2 H), 1.90 (dt, *J* = 9.6, 6.7 Hz, 1 H), 1.47 (dd, *J* = 9.0, 4.3 Hz, 1 H), 1.22 (s, 3 H), 0.88-0.82 (bm, 1 H); ^{13}C NMR δ 173.69, 171.89, 155.97, 141.66, 136.42, 135.80, 129.19, 128.71, 128.54, 128.48, 128.08, 128.00, 127.56, 127.13, 126.63, 66.86, 54.99, 53.34, 52.23, 37.65, 30.44, 24.17, 20.44, 14.43; MS (ESI) *m/z* (intensity) 523 ($[M+Na]^+$, 100); HRMS (ESI) *m/z* calculated for $C_{30}H_{32}N_2O_5Na$ (M+Na) 523.2209, found 523.2219.



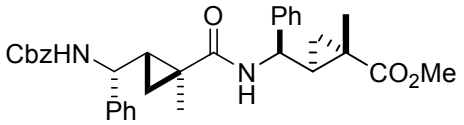
(-)-**393**

Cbz-*D*-$^{\alpha}$MeΔPhg-*D*-$^{\alpha}$MeΔPhg-OMe ((-)-393). Saponification of (-)-**379**: To a solution of (-)-**379** (45 mg, 0.13 mmol) in MeOH (0.50 mL) was added 2N NaOH (0.50 mL) and THF (0.20 mL). The reaction mixture was stirred for 2 h, acidified with 10% HCl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated.

N-Cbz deprotection of (-)-**379**: A round bottom flask containing a mixture of (-)-**379** (49 mg, 0.14 mmol) and 10% Pd/C (15 mg, 14 μmol) was evacuated, purged with N_2 and suspended in MeOH (1.5 mL). The flask was evacuated and purged with H_2 (1 atm), and stirred under an atmosphere of H_2 for 1 h. The mixture was filtered through Celite and concentrated.

Fragment Coupling: The acid and amine were dissolved in dry CH_2Cl_2 and concentrated into a 10 mL round bottom flask. The residue was dissolved in dry DMF (1.0 mL), cooled to 0 °C, treated with BOP (67 mg, 0.15 mmol) and DIPEA (33 μL, 0.19 mmol), warmed slowly to r.t. and stirred for 10 h. The reaction mixture was diluted with EtOAc, washed with water, 10% HCl and brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on

deactivated SiO_2 (13:7, hexanes/EtOAc containing 1% v/v Et_3N) to give (-)-**393** (63 mg, 91%) as a colorless foam: $[\alpha]_D$ -70.9 (*c* 1.0, $CHCl_3$); IR (KBr) 3348, 3031, 2951, 1708, 1625, 1522, 1455, 1306, 1286, 1258, 1198, 1167 cm^{-1}; ^1H NMR δ 7.40-7.27 (m, 15 H), 6.20 (d, *J* = 8.6 Hz, 1 H), 5.59 (d, *J* = 8.2 Hz, 1 H), 5.12, 5.10 (AB, *J* = 12.2 Hz, 2 H), 4.86 (t, *J* = 9.7 Hz, 1 H), 4.53 (t, *J* = 9.5 Hz, 1 H), 3.66 (s, 3 H), 2.02-1.89 (m, 2 H), 1.55 (dd, *J* = 9.0, 4.2 Hz, 1 H), 1.36 (dd, *J* = 9.0, 4.1 Hz, 1 H), 1.29 (s, 3 H), 1.28 (s, 3 H), 0.87 (bm, 1 H), 0.81 (dd, *J* = 6.4, 4.4 Hz, 1 H); ^{13}C NMR δ 175.56, 173.49, 156.02, 141.96, 141.45, 136.45, 128.72, 128.64, 128.43, 128.02, 127.94, 127.60, 127.49, 126.61, 126.49, 66.79, 54.88, 52.53, 52.08, 31.33, 30.81, 24.04, 23.98, 20.73, 20.30, 14.69, 14.16; MS (EI) *m/z* (intensity) 540 (M^+, 47), 332 (16), 330 (19), 171 (40), 143 (100); HRMS (EI) *m/z* calculated for $C_{33}H_{36}N_2O_5$ 540.2624, found 540.2610.

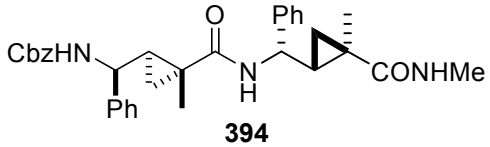


(+)-**393**

Cbz-*L*-$^{\alpha}$MeΔPhg-*L*-$^{\alpha}$MeΔPhg-OMe ((+)-393). Saponification of (+)-**379**: To a solution of (+)-**379** (0.12 g, 0.34 mmol) in MeOH (1.5 mL) was added THF (0.20 mL) and 2N NaOH (1.5 mL). The reaction mixture was stirred for 4 h, acidified with 10% HCl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated.

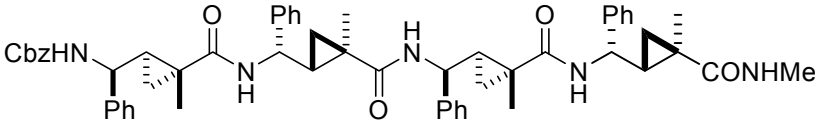
N-Cbz-Deprotection of (+)-**379**: To a mixture of (+)-**379** (0.10 g, 0.30 mmol) and 10% Pd/C (32 mg, 0.030 mmol) under N_2 was added MeOH (3 mL). The flask was evacuated, purged with H_2 (1 atm), and vigorously stirred under an atmosphere of H_2 for 1 h. The mixture was filtered through Celite and concentrated into a flask containing the acid prepared above.

Fragment coupling: The mixture of amine and acid was dissolved in dry DMF (2.0 mL), cooled to 0 °C and treated with BOP (0.23 g, 0.51 mmol) and DIPEA (78 μL, 0.45 mmol). The solution was warmed to r.t., stirred for 10 h, diluted with EtOAc and washed with H_2O, 10% HCl and brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (2:1, hexanes/EtOAc containing 1% v/v Et_3N) to give (+)-**393** (0.13 g, 80%) as a colorless solid: $[\alpha]_D$ +75.6 (*c* 0.84, $CHCl_3$).



394

Cbz-*D*-$^{\alpha}$MeΔPhg-*D*-$^{\alpha}$MeΔPhg-NHMe (394). To a solution of (-)-**393** (50 mg, 0.092 mmol) in dry Et_2O (1.0 mL) was added KOTMS (95 mg, 0.74 mmol). The reaction mixture was stirred for 12 h, acidified with 10% HCl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was dissolved in dry CH_2Cl_2 (1.0 mL), treated with EDCI (21 mg, 0.11 mmol), $MeNH_2$•HCl (37 mg, 0.56 mmol), DMAP (1.0 mg, 7.1 μmol), and DIPEA (48 μL, 0.28 mmol), stirred for 12 h and diluted with EtOAc. The solution was washed with 10% HCl, H_2O and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (EtOAc containing 1% v/v Et_3N) to afford **394** (31 mg, 62%) as a colorless foam: $[\alpha]_D$ -88.0 (*c* 0.15, $CHCl_3$); IR (KBr) 3032 2928, 1700, 1653, 1635, 1522, 1258, 1206 cm^{-1}; ^1H NMR (500 MHz) δ 7.37-7.27 (m, 15 H), 6.12 (d, *J* = 8.0 Hz, 1 H), 5.75 (d, *J* = 3.9 Hz, 1 H), 5.22 (d, *J* = 7.7 Hz, 1 H), 5.15-5.10 (m, 2 H), 4.86 (t, *J* = 9.6 Hz, 1 H), 4.53 (bt, 1 H), 2.84 (d, *J* = 4.6 Hz, 3 H), 2.00-1.89 (m, 2 H), 1.56-1.55 (m, 1 H), 1.42-1.41 (m, 1 H), 1.31 (s, 3 H), 1.29 (s, 3 H), 0.94-0.88 (m, 1 H), 0.77-0.73 (m, 1 H); ^{13}C NMR (125 MHz) δ 174.72, 173.60, 155.99, 141.68, 136.38, 128.76, 128.52, 128.14, 128.06, 127.79, 127.52, 126.70, 126.61, 66.91, 54.86, 52.84, 30.81, 30.24, 26.91, 24.22, 24.02, 20.30, 20.00, 14.73, 14.60; MS (ESI) *m/z* (intensity) 562 ($[M+Na]^+$, 100); HRMS (ESI) *m/z* calculated for $C_{33}H_{37}N_3O_4Na$ (M+Na) 562.2682, found 562.2684.



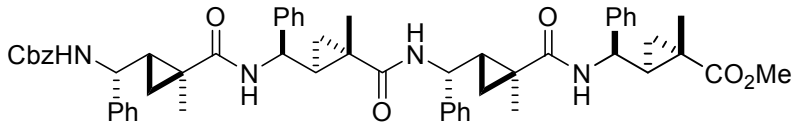
397

Cbz-*D*-$^{\alpha}$MeΔPhg-*D*-$^{\alpha}$MeΔPhg-*D*-$^{\alpha}$MeΔPhg-*D*-$^{\alpha}$MeΔPhg-NHMe (397). Saponification of (-)-**393**: To a solution of (-)-**393** (28 mg, 52 μmol) in dry Et_2O (1.0 mL) was added KOTMS (53 mg, 0.41 mmol). The reaction mixture was stirred for 12 h, acidified with 10% HCl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated.

N-Cbz deprotection of **394**: A round bottom flask containing a mixture of **394** (31 mg, 57 μmol) and 10% Pd/C (6.0 mg, 5.7 μmol) was evacuated, purged with N_2, suspended in MeOH (1.0

mL), evacuated and purged with H_2 (1 atm) and stirred under an atmosphere of H_2 for 1 h. The mixture was filtered through Celite and concentrated.

Fragment coupling: The amine and acid were concentrated into a 25 mL flask and dissolved in dry DMF (1.0 mL). The mixture was treated at 0 °C with BOP (27 mg, 62 μmol) and DIPEA (11 μL, 65 μmol), warmed to r.t., stirred for 10 h, diluted with EtOAc and washed with water, 10% HCl and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (EtOAc containing 1% v/v Et_3N) to give **397** (29 mg, 62%) as a colorless foam: $[\alpha]_D$ -105.9 (*c* 0.44, $CHCl_3$); IR (KBr) 3399, 3030, 2939, 1718, 1654, 1638, 1508, 1193 cm^{-1}; ^1H NMR δ 7.36-7.24 (m, 25 H), 6.38-6.25 (m, 3 H), 5.79-5.78 (m, 1 H), 5.53 (bd, *J* = 7.9 Hz, 1 H), 5.16-5.07 (m, 2 H), 4.93-4.84 (m, 3 H), 4.52 (bt, *J* = 9.1 Hz, 1 H), 2.80 (d, *J* = 4.7 Hz, 3 H), 2.07-1.87 (m, 4 H), 1.56-1.40 (m, 4 H), 1.29 (s, 3 H), 1.25 (s, 6 H), 1.22 (s, 3 H), 0.89-0.86 (m, 1 H), 0.78-0.70 (m, 3 H); ^{13}C NMR δ 174.65, 173.67, 173.62, 156.02, 141.86, 141.73, 141.68, 141.61, 136.49, 128.78, 128.74, 128.49, 128.08, 128.00, 127.70, 127.63, 127.52, 126.73, 126.65, 66.86, 54.96, 52.92, 52.53, 52.49, 30.89, 30.30, 26.87, 24.31, 24.24, 24.09, 20.43, 20.00, 19.76, 14.74, 14.62; MS (ESI) *m/z* (intensity) 936 ($[M+Na]^+$, 34), 914 ($[M+H]^+$, 100), 763 (24), 596 (40), 562 (44), 382 (60), 202 (83); HRMS (ESI) *m/z* calculated for $C_{57}H_{63}N_5O_6Na$ (M+Na) 936.4676, found 936.4653.

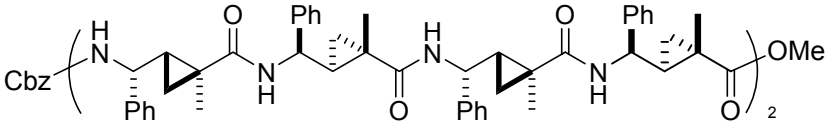


398

Cbz-*L*-$^{\alpha}$MeΔPhg-*L*-$^{\alpha}$MeΔPhg-*L*-$^{\alpha}$MeΔPhg-*L*-$^{\alpha}$MeΔPhg-OMe (398). Saponification of (+)-**393**: To a solution of (+)-**393** (67 mg, 0.12 mmol) in MeOH (1.0 mL) was added THF (0.20 mL) and 2N NaOH (1.0 mL). The reaction was stirred for 4 h, acidified with 10% HCl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated.

N-Cbz-Deprotection of (+)-**393**: To a mixture of (+)-**393** (70 mg, 0.13 mmol) and 10% Pd/C (14 mg, 0.013 mmol) under N_2 was added MeOH (1.5 mL). The flask was evacuated, purged with H_2 (1 atm), and the mixture was vigorously stirred under an atmosphere of H_2 for 2 h. The mixture was filtered through Celite and concentrated into a flask containing the acid prepared above.

Fragment coupling: The mixture of amine and acid was dissolved in dry DMF (1.5 mL), cooled to 0 °C, treated with BOP (82 mg, 0.19 mmol) and DIPEA (34 μL, 0.19 mmol), warmed to r.t. and stirred for 10 h. The solution was diluted with EtOAc and washed with H_2O, 10% HCl and brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (2:3, hexanes/EtOAc containing 1% v/v Et_3N) to give **398** (82 mg, 73%) as a colorless solid: mp 159.4-161.0 °C (hexanes/EtOAc); $[\alpha]_D$ +109.7 (*c* 0.66, $CHCl_3$); IR (KBr) 3422, 3031, 2951, 1719, 1654, 1646, 1637, 1508, 1499, 1458, 1306, 1258, 1194 cm^{-1}; ^1H NMR δ 7.38-7.28 (m, 25 H), 6.19-6.12 (m, 3 H), 5.31 (bd, *J* = 8.4 Hz, 1 H), 5.13, 5.12 (AB, *J* = 12.3 Hz, 2 H), 4.96-4.86 (m, 3 H), 4.53 (bt, *J* = 9.6 Hz, 1 H), 3.69 (s, 3 H), 2.00-1.86 (m, 4 H), 1.58-1.42 (m, 4 H), 1.34 (s, 3 H), 1.31 (s, 3 H), 1.27 (s, 6 H), 0.95-0.78 (m, 4 H); ^{13}C NMR δ 175.56, 173.72, 173.58, 156.06, 141.92, 141.68, 141.36, 136.49, 128.78, 128.68, 128.44, 128.02, 127.96, 127.59, 126.66, 126.60, 126.50, 66.77, 54.89, 52.60, 52.45, 52.14, 31.40, 30.84, 30.81, 24.25, 24.05, 23.99, 20.74, 20.35, 19.73, 14.67, 14.55, 14.48, 14.22; MS (ESI) *m/z* (intensity) 953 ($[M+K]^+$, 100), 937 ($[M+Na]^+$, 85), 915 ($[M+H]^+$, 30); HRMS (ESI) *m/z* calculated for $C_{57}H_{63}N_4O_7$ (M+H) 915.4697, found 915.4730.



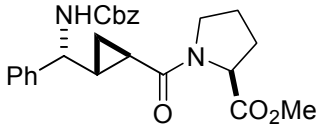
399

Cbz-*L*-$^{\alpha}$MeΔPhg-*L*-$^{\alpha}$MeΔPhg-*L*-$^{\alpha}$MeΔPhg-*L*-$^{\alpha}$MeΔPhg-OMe-*L*-$^{\alpha}$MeΔPhg-*L*-$^{\alpha}$MeΔPhg-*L*-$^{\alpha}$MeΔPhg-*L*-$^{\alpha}$MeΔPhg-OMe (399). Saponification of **398**: To a solution of **398** (32 mg, 35 μmol) in MeOH (0.50 mL) was added THF (0.20 mL) and 2N NaOH (0.50 mL). The reaction mixture was stirred for 4 h, acidified with 10% HCl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated.

N-Cbz-Deprotection of **398**: To a mixture of **398** (36 mg, 39 μmol) and 10% Pd/C (4.0 mg, 3.9 μmol) under N_2 was added MeOH (1.0 mL). The flask was evacuated, purged with H_2 (1 atm), and the mixture was vigorously stirred under an atmosphere of H_2 for 2 h. The suspension was filtered through Celite and concentrated into a flask containing the acid prepared above.

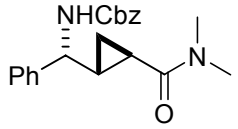
Fragment coupling: The amine and acid were dissolved in dry DMF (1.0 mL), cooled to 0 °C and treated with BOP (23 mg, 52 μmol) and DIPEA (9.0 μL, 52 μmol). The reaction mixture was warmed to r.t., stirred for 10 h, diluted with EtOAc and washed with H_2O, 10% HCl and

brine, dried (Na_2SO_4) and concentrated to give crude **399**. ^{1}H NMR δ 7.36-7.77 (m, 45 H), 6.17-6.08 (m, 7 H), 5.25 (d, *J* = 8.6 Hz, 1 H), 5.17-5.08 (m, 2 H), 4.97-4.87 (m, 7 H), 4.53 (t, *J* = 10.5 Hz, 1 H), 3.70 (s, 3 H), 2.03-1.90 (m, 8 H), 1.57-1.49 (m, 8 H), 1.35-1.26 (m, 24 H), 0.93-0.87 (m, 8 H).



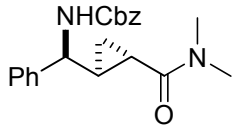
401

Cbz-*L*-H$_2$ΔPhg-*L*-Pro-OMe (401). To a solution of (-)-**365** (35 mg, 0.10 mmol) in dry Et_2O (1.0 mL) was added KOTMS (26 mg, 0.21 mmol). The reaction mixture was stirred for 6 h, quenched with 10% HCl, extracted with CH_2Cl_2 (3x), and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was dissolved in dry CH_2Cl_2 (1.0 mL) and treated at 0 °C with EDCI (24 mg, 0.12 mmol), DMAP (1.0 mg, 0.010 mmol), DIPEA (0.11 mL, 0.62 mmol) and *L*-Pro-OMe•HCl (34 mg, 0.21 mmol). The solution was warmed to r.t., stirred for 12 h, diluted with H_2O and extracted with CH_2Cl_2 (2x) and EtOAc (2x), and the combined organic layers were washed with 10% HCl (2x) and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (19:1, CH_2Cl_2/acetone containing 1% v/v Et_3N) to afford **401** (38 mg, 84%) as a colorless oil: $[\alpha]_D$ -68.2 (*c* 0.76, $CHCl_3$); IR (neat) 3315, 3063, 3030, 2953, 1742, 1712, 1627, 1528, 1456, 1236 cm^{-1}; ^{1}H NMR (3.5:1 mixture of amide bond rotamers) major rotamer δ 7.36-7.31 (m, 10 H), 5.34 (d, *J* = 8.1 Hz, 1 H), 5.17 (d, *J* = 12.3 Hz, 1 H), 5.03 (d, *J* = 12.3 Hz, 1 H), 4.46 (dd, *J* = 8.2, 4.0 Hz, 1 H), 4.26 (t, *J* = 8.9 Hz, 1 H), 3.77-3.74 (m, 1 H), 3.70 (s, 3 H), 3.65-3.55 (m, 1 H), 2.35-1.79 (m, 5 H), 1.35-1.27 (m, 2 H), 0.91-0.84 (m, 1 H); minor rotamer (representative signals) δ 5.54-5.52 (m, 1 H), 4.61 (dd, *J* = 8.3, 2.8 Hz, 1 H), 4.12-4.06 (m, 1 H); ^{13}C NMR δ 172.77, 171.05, 155.82, 140.69, 136.40, 128.67, 128.46, 128.10, 127.96, 127.72, 126.62, 66.69, 58.76, 58.14, 52.11, 46.87, 29.17, 27.01, 24.61, 22.51, 19.42, 13.55; MS (EI) *m/z* (intensity) 436 (M^+, 2), 377 (6), 128 (25), 91 (100); HRMS (EI) *m/z* calculated for $C_{25}H_{28}N_2O_5$ 436.1998, found 436.2010.



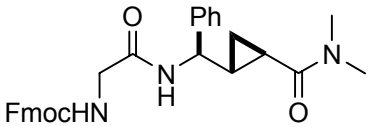
(-)-**403**

Cbz-*L*-H_2ΔPhg-NMe_2 ((-)-403). To a solution of (-)-**365** (35 mg, 0.10 mmol) in dry Et_2O (1.0 mL) was added KOTMS (26 mg, 0.21 mmol). The reaction mixture was stirred for 6 h, quenched with 10% HCl, extracted with CH_2Cl_2 (3x), and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was dissolved in dry CH_2Cl_2 (1.0 mL) and treated at 0 °C with EDCI (24 mg, 0.12 mmol), DMAP (1.0 mg, 0.010 mmol), DIPEA (0.11 mL, 0.62 mmol) and Me_2NH•HCl (25 mg, 0.31 mmol). The solution was warmed to r.t., stirred for 12 h, diluted with H_2O and extracted with CH_2Cl_2 (2x) and EtOAc (2x). The combined organic layers were washed with 10% HCl (2x) and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (19:1, CH_2Cl_2/acetone containing 1% v/v Et_3N) to afford (-)-**403** (31 mg, 85%) as a colorless oil: $[\alpha]_D$ -28.1 (*c* 0.62, $CHCl_3$); IR (neat) 3283, 3031, 2928, 1710, 1624, 1529, 1497, 1257 cm^{-1}; ^1H NMR δ 7.37-7.27 (m, 10 H), 5.43 (bd, *J* = 8.0 Hz, 1 H), 5.15, 5.05 (AB, *J* = 12.3 Hz, 2 H), 4.24 (t, *J* = 9.1 Hz, 1 H), 3.05 (s, 3 H), 2.93 (s, 3 H), 2.10-2.07 (m, 1 H), 1.86-1.78 (m, 1 H), 1.30-1.24 (m, 1 H), 0.89-0.81 (m, 1 H); ^{13}C NMR δ 172.13, 155.90, 140.87, 136.44, 128.65, 128.46, 128.08, 128.00, 127.67, 126.63, 66.73, 58.28, 37.06, 35.80, 26.94, 17.97, 13.34; MS (EI) *m/z* (intensity) 352 (M^+, 3), 91 (100); HRMS (EI) *m/z* calculated for $C_{21}H_{24}N_2O_3$ 352.1787, found 352.1792.



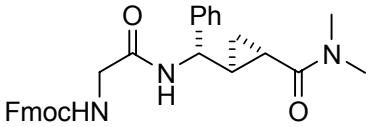
(+)-**403**

Cbz-*D*-H_2ΔPhg-NMe_2 ((+)-403). According to the protocol for the preparation of (-)-**403**, (+)-**365** (40 mg, 0.12 mmol), KOTMS (30 mg, 0.24 mmol) in Et_2O (1.0 mL), EDCI (27 mg, 0.14 mmol), DMAP (2.0 mg, 0.012 mmol), DIPEA (0.13 mL, 0.71 mmol) and Me_2NH•HCl (29 mg, 0.35 mmol) afforded (+)-**403** (36 mg, 86%) as a colorless oil: $[\alpha]_D$ +27.4 (*c* 0.56, $CHCl_3$).



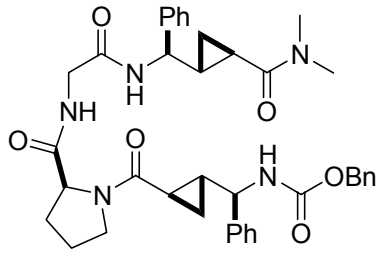
(-)-**405**

Fmoc-Gly-*L*-H_2ΔPhg-NMe_2 ((-)-405). A flask containing a mixture of (-)-**403** (30 mg, 0.085 mmol) and Pd/C (9.0 mg, 0.0085 mmol, 10 wt% Pd/C) in MeOH (2.0 mL) was evacuated and purged with H_2 (1 atm). The suspension was stirred under an atmosphere of H_2 for 1.5 h, filtered through Celite and concentrated. The residue was dissolved in dry DMF (1.0 mL), cooled to 0 °C, treated with Fmoc-Gly-OH (51 mg, 0.17 mmol), BOP (45 mg, 0.10 mmol) and DIPEA (18 μL, 0.10 mmol), stirred for 30 min, and warmed to r.t. After stirring for 4 h, the reaction mixture was diluted with H_2O and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (7:3, CH_2Cl_2/acetone containing 1% v/v Et_3N) to afford (-)-**405** (31 mg, 73%) as a colorless oil: $[\alpha]_D$ -21.5 (*c* 0.63, $CHCl_3$); IR (neat) 3416, 3290, 3065, 3009, 2926, 2854, 1722, 1667, 1621, 1538, 1248, 1154 cm^{-1}; ^1H NMR δ 7.76 (d, *J* = 7.5 Hz, 2 H), 7.57 (d, *J* = 7.3 Hz, 2 H), 7.40 (t, *J* = 7.4 Hz, 2 H), 7.35-7.23 (m, 7 H), 7.10 (bd, *J* = 7.8 Hz, 1 H), 5.67-5.63 (m, 1 H), 4.51 (t, *J* = 9.2 Hz, 1 H), 4.37 (d, *J* = 7.0 Hz, 2 H), 4.18 (t, *J* = 7.0 Hz, 1 H), 3.92, 3.85 (AB of ABX, J_{AB} = 16.9 Hz, J_{AX} = 5.5 Hz, J_{BX} = 5.2 Hz, 2 H), 3.11 (s, 3 H), 2.90 (s, 3 H), 2.08-2.03 (m, 1 H), 1.89-1.86 (m, 1 H), 1.32-1.20 (m, 1 H), 0.91-0.85 (m, 1 H); ^{13}C NMR δ 172.20, 168.20, 156.47, 147.42, 143.66, 141.23, 140.58, 128.68, 127.72, 127.04, 126.69, 124.99, 119.96, 67.13, 56.28, 46.98, 44.41, 37.25, 35.84, 26.33, 18.20, 13.71; MS (EI) *m/z* (intensity) 497 (M^+, 0.2), 178 (100); HRMS (EI) *m/z* calculated for $C_{30}H_{31}N_3O_4$ 497.2315, found 497.2330.



(+)-**405**

Fmoc-Gly-*D*-H_2ΔPhg-NMe_2 ((+)-405). According to the protocol for the preparation of (-)-**405**, (+)-**403** (24 mg, 0.068 mmol), Pd/C (7.0 mg, 6.8 μmol) in MeOH (1.0 mL), BOP (33 mg, mmol), DIPEA (13 μL, 0.074 mmol) and Fmoc-Gly-OH (61 mg, 0.21 mmol) afforded (+)-**405** (26 mg, 76%) as a colorless oil: $[\alpha]_D$ + 20.5 (*c* 0.58, $CHCl_3$).

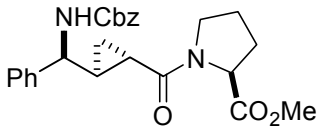


408

Cbz-*L*-H_2ΔPhg-*L*-Pro-OMe-Gly-*L*-H_2ΔPhg-NMe_2 (408). Saponification of **401**: To a solution of **401** (38 mg, 0.087 mmol) in dry Et_2O (1.0 mL) was added KOTMS (22 mg, 0.17 mmol). The reaction mixture was stirred for 12 h, acidified with 10% HCl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated.

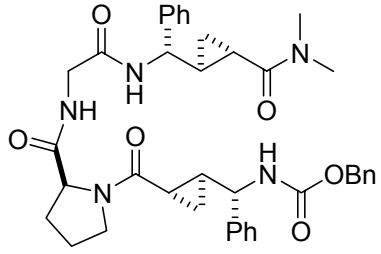
N-Fmoc deprotection of (-)-**405**: To a solution of (-)-**405** (31 mg, 0.062 mmol) in dry DMF (0.90 mL) was added piperidine (0.10 mL). The mixture was stirred for 1 h, concentrated and the residue was dissolved in dry toluene (ca. 10 mL) and concentrated (repeat 10 times) to give a yellow/orange solid.

Fragment coupling: The amine and acid were concentrated into a 25 mL flask. The residue was dissolved in dry CH_2Cl_2 (1.0 mL), treated with DMAP (1.0 mg, 0.0087 mmol) and EDCI (18 mg, 0.096 mmol), and the reaction mixture wasc stirred for 12 h, diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were washed with 10% HCl (2x) and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (3:2, CH_2Cl_2/acetone containing 1% Et_3N) to afford **408** (25 mg, 60%): $[\alpha]_D$ -55.4 (*c* 0.28, $CHCl_3$); IR (KBr) 3420, 3282, 3031, 2928, 1720, 1683, 1647, 1621, 1530, 1455, 1259 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.31 (t, *J* = 6.2 Hz, 1 H), 8.04 (d, *J* = 8.7 Hz, 1 H), 7.97 (d, *J* = 8.8 Hz, 1 H), 7.34-7.15 (m, 15 H), 5.08 (d, *J* = 12.5 Hz, 1 H), 4.95 (d, *J* = 12.6 Hz, 1 H), 4.60 (t, *J* = 8.1 Hz, 1 H), 4.22-4.13 (m, 1 H), 4.19 (t, *J* = 8.9 Hz, 1 H), 3.68-3.63 (m, 1 H), 3.64 (d, *J* = 5.7 Hz, 1 H), 3.57-3.49 (m, 1 H), 3.38-3.31 (m, 1 H), 3.02 (s, 3 H), 2.75 (s, 3 H), 2.07-1.98 (m, 2 H), 1.95-1.90 (m, 2 H), 1.83-1.78 (m, 2 H), 1.53-1.41 (m, 2 H), 0.96-0.90 (m, 1 H), 0.84-0.74 (m, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.99, 171.20, 170.97, 168.15, 155.68, 142.46, 142.31, 137.11, 128.28, 128.23, 128.08, 127.76, 127.63, 126.94, 126.81, 126.46, 126.40, 65.26, 60.29, 56.93, 53.68, 47.06, 42.17, 36.71, 35.15, 29.19, 27.75, 26.35, 24.29, 18.86, 16.25, 12.35, 11.89; MS (ESI) *m/z* (intensity) 702 ($[M+Na]^+$, 100); HRMS (ESI) *m/z* calculated for $C_{39}H_{45}N_5O_6Na$ (M+Na) 702.3268, found 702.3301.



409

Cbz-*D*-H_2ΔPhg-*L*-Pro-OMe (409). To a solution of (+)-**365** (40 mg, 0.12 mmol) in dry Et_2O (1.0 mL) was added KOTMS (30 mg, 0.24 mmol). The reaction mixture was stirred for 6 h, quenched with 10% HCl and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was dissolved in dry CH_2Cl_2 (1.0 mL) and treated at 0 °C with EDCI (27 mg, 0.14 mmol), DMAP (2.0 mg, 0.012 mmol), DIPEA (0.13 mL, 0.71 mmol) and *L*-Pro-OMe•HCl (59 mg, 0.35 mmol). The reaction mixture was warmed to r.t., stirred for 12 h, diluted with H_2O and extracted with CH_2Cl_2 (2x) and EtOAc (2x). The combined organic layers were washed with 10% HCl (2x) and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (19:1, CH_2Cl_2/acetone containing 1% v/v Et_3N) to afford **409** (39 mg, 76%) as a colorless oil: $[\alpha]_D$ -13.1 (*c* 0.67, $CHCl_3$); IR (neat) 3301, 3030, 2953, 1713, 1626, 1530, 1455, 1433, 1237, 1200, 1176 cm^{-1}; ^1H NMR (2.3:1 mixture of amide bond rotamers) major rotamer δ 7.36-7.27 (m, 10 H), 5.51 (d, *J* = 8.3 Hz, 1 H), 5.17 (d, *J* = 12.3 Hz, 1 H), 5.05 (d, *J* = 12.3 Hz, 1 H), 4.46 (dd, *J* = 8.3, 3.8 Hz, 1 H), 4.28 (t, *J* = 8.9 Hz, 1 H), 3.73 (s, 3 H), 3.71-3.48 (m, 2 H), 2.21-2.11 (m, 1 H), 2.07-1.91 (m, 2 H), 1.89-1.87 (m, 1 H), 1.32-1.26 (m, 1 H), 0.90-0.83 (m, 1 H); ^{13}C NMR (major rotamer) δ 172.84, 170.95, 155.97, 140.95, 136.49, 128.63, 128.46, 128.01, 127.94, 127.64, 126.62, 66.75, 58.85, 58.10, 52.06, 46.85, 29.17, 27.03, 24.65, 19.24, 13.19; MS (EI) *m/z* (intensity) 436 (M^+, 3), 377 (10), 269 (5), 128 (50), 91 (95), 70 (100); HRMS (EI) *m/z* calculated for $C_{25}H_{28}N_2O_5$ 436.1998, found 436.2015.



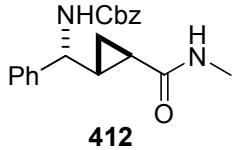
411

Cbz-*D*-H_2ΔPhg-*L*-Pro-OMe-Gly-*D*-H_2ΔPhg-NMe_2 (411). Saponification of (+)-**405**: To a solution of (+)-**405** (33 mg, 0.076 mmol) in dry Et_2O (1.0 mL) was added KOTMS (19 mg, 0.15 mmol). The reaction mixture was stirred for 12 h, acidified with 10% HCl and extracted with

EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated.

N-Fmoc deprotection of **409**: To a solution of **409** (44 mg, 0.088 mmol) in dry DMF (0.90 mL) was added piperidine (0.10 mL). The reaction mixture was stirred for 1 h and concentrated. The residue was dissolved in dry toluene (ca. 10 mL) and concentrated (repeated 10 times) to afford a light yellow solid.

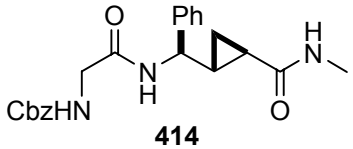
Fragment coupling: The amine and acid were concentrated into a 25 mL flask and the residue was dissolved in dry CH_2Cl_2 (1.0 mL), treated with DMAP (1.0 mg, 0.0087 mmol) and EDCI (17 mg, 0.089 mmol) and stirred for 12 h. The mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were washed with 10% HCl (2x) and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (3:2, CH_2Cl_2/acetone containing 1% Et_3N) to afford **411** (24 mg, 49%) as a colorless solid: $[\alpha]_D$ +74.0 (*c* 0.26, $CHCl_3$); IR (neat) 3291, 2923, 2852, 1716, 1695, 1619, 1540, 1456, 1258, 1155 cm^{-1}; ^1H NMR (3:1 mixture of amide bond rotamers, DMSO-d_6) major rotamer δ 8.42 (t, *J* = 5.6 Hz, 1 H), 8.20 (d, *J* = 9.0 Hz, 1 H), 8.17 (d, *J* = 8.7 Hz, 1 H), 7.42-7.17 (m, 15 H), 5.05 (d, *J* = 12.5 Hz, 1 H), 4.91 (d, *J* = 12.5 Hz, 1 H), 4.42 (t, *J* = 9.4 Hz, 1 H), 4.18-4.08 (m, 1 H), 4.11 (t, *J* = 9.0 Hz, 1 H), 3.82 (dd, *J* = 16.9, 6.8 Hz, 1 H), 3.67-3.46 (m, 3 H), 3.06 (s, 3 H), 2.72 (s, 3 H), 2.02-1.93 (m, 2 H), 1.91-1.81 (m, 3 H), 1.67-1.49 (m, 2 H), 0.98-0.80 (m, 5 H); minor rotamer (representative signals) δ 8.52 (d, *J* = 8.5 Hz, 1 H), 8.05 (d, *J* = 8.5 Hz, 1 H), 3.08 (s, 3 H), 2.80 (s, 3 H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 172.44, 172.35, 172.10, 168.39, 156.46, 142.60, 141.18, 136.79, 128.47, 128.43, 128.23, 128.13, 127.77, 127.28, 127.12, 126.99, 126.63, 66.35, 61.06, 59.35, 56.15, 47.62, 43.19, 37.52, 36.10, 29.21, 28.23, 28.06, 25.12, 20.06, 17.74, 14.99, 8.45; MS (ESI) *m/z* (intensity) 702 ($[M+Na]^+$, 100); HRMS (ESI) *m/z* calculated for $C_{39}H_{45}N_5O_6Na$ (M+Na) 702.3268, found 702.3254.



412

Cbz-*L*-H_2ΔPhg-NHMe (412). To a solution of (-)-**365** (0.10 g, 0.31 mmol) in dry Et_2O (4.0 mL) was added KOTMS (79 mg, 0.62 mmol). The reaction mixture was stirred for 7 h, acidified with 10% HCl and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was dissolved in dry CH_2Cl_2 (3.0 mL), treated

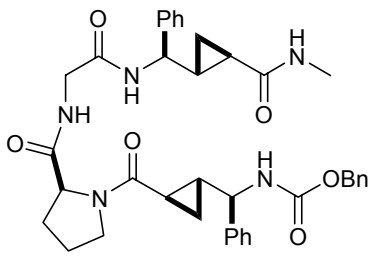
with EDCI (74 mg, 0.39 mmol), DMAP (4.0 mg, 0.033 mmol), DIPEA (0.16 mL, 0.93 mmol), and $MeNH_2$•HCl (0.10 g, 1.6 mmol), stirred for 12 h, diluted with H_2O and extracted with EtOAc. The combined organic layers were washed with 10% HCl, H_2O and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (EtOAc containing 1% v/v Et_3N) to afford **412** (75 mg, 72%) as a colorless solid: mp 200.7-202.9 °C (hexanes/EtOAc); $[\alpha]_D$ -41.1 (*c* 0.45, $CHCl_3$); IR (KBr) 3315, 1686, 1640, 1554, 1260 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.44-7.41 (m, 2 H), 7.35-7.16 (m, 10 H), 5.08, 5.01 (AB, *J* = 12.6 Hz, 2 H), 4.16 (t, *J* = 8.5 Hz, 1 H), 2.68 (d, *J* = 4.7 Hz, 3 H), 1.74-1.66 (m, 2 H), 1.01-0.95 (m, 1 H), 0.85-0.79 (m, 1 H); ^{13}C NMR δ 172.70, 155.93, 140.81, 136.38, 128.69, 128.49, 128.14, 128.11, 127.74, 126.62, 66.77, 58.31, 26.51, 26.15, 21.69, 12.51; MS (EI) *m/z* (intensity) 338 (M^+, 3), 247 (8), 91 (100); HRMS (EI) *m/z* calculated for $C_{20}H_{22}N_2O_3$ 338.1630, found 338.1631.



414

Cbz-Gly-*L*-H_2ΔPhg-NHMe (414). A suspension of **412** (73 mg, 0.22 mmol) and Pd/C (23 mg, 0.022 mmol, 10 wt% Pd/C) in N_2 purged MeOH (3.0 mL) was evacuated and purged with H_2. The reaction mixture was vigorously stirred under an atmosphere of H_2 for 1.5 h, filtered through Celite and concentrated. The residue was dissolved in dry DMF (2.0 mL), cooled to 0 °C and treated with Cbz-Gly-OH (90 mg, 0.43 mmol), BOP (210 mg, 0.48 mmol) and DIPEA (83 μL, 0.32 mmol). The mixture was stirred for 30 min, warmed to r.t., stirred for 10 h, diluted with EtOAc, washed with H_2O (4x), 10% HCl and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (1:1, CH_2Cl_2/acetone containing 1% v/v Et_3N) to afford **414** (68 mg, 80%) as a colorless foam: $[\alpha]_D$ -16.0 (*c* 0.93, MeOH); IR (KBr) 3296, 3064, 3032, 2927, 1713, 1646, 1544, 1245, 1159 cm^{-1}; ^1H NMR δ 7.45 (d, *J* = 8.2 Hz, 1 H), 7.37-7.27 (m, 10 H), 6.57-6.56 (m, 1 H), 5.84 (t, *J* = 5.7 Hz, 1 H), 5.10-5.02 (m, 2 H), 4.39 (t, *J* = 9.1 Hz, 1 H), 3.91 (dd, *J* = 16.6, 5.9 Hz, 1 H), 3.71 (dd, *J* = 16.6, 5.4 Hz, 1 H), 2.71 (d, *J* = 4.7 Hz, 3 H), 1.76-1.67 (m, 1 H), 1.62-1.59 (m, 1 H), 1.30-1.23 (m, 1 H), 0.84-0.78 (m, 1 H); ^{13}C NMR δ 172.96, 168.67, 156.80, 140.79, 136.18, 128.66, 128.54, 128.21, 127.90, 127.62, 126.56, 67.10, 56.39, 44.58, 26.45, 26.12, 21.30, 13.33; MS (EI) *m/z* (intensity) 395 (M^+, 23),

337 (24), 203 (94), 188 (74), 131 (100); HRMS (EI) *m/z* calculated for $C_{22}H_{25}N_3O_4$ 395.1845, found 395.1834.



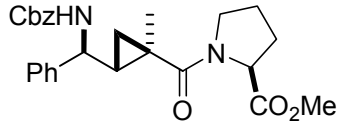
415

Cbz-*L*-H$_2$ΔPhg-*L*-Pro-OMe-Gly-*L*-H$_2$ΔPhg-NHMe (415). Saponification of **401**: To a solution of **401** (58 mg, 0.13 mmol) in dry Et_2O (1.5 mL) was added KOTMS (34 mg, 0.27 mmol). The reaction mixture was stirred for 12 h, acidified with 10% HCl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated.

N-Cbz deprotection of **414**: To a mixture of **414** (68 mg, 0.17 mmol) and Pd/C (18 mg, 0.017 mmol, 10 wt% Pd/C) was added under N_2 MeOH (2.0 mL). The suspension was evacuated and purged with H_2 and the mixture was vigorously stirred under an atmosphere of H_2 for 1.5 h, filtered through Celite and concentrated.

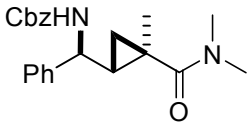
Fragment coupling: The amine and acid were concentrated into a 25 mL flask and the residue was dissolved in dry DMF (2.0 mL), cooled to 0 °C and treated with BOP (83 mg, 0.19 mmol) and DIPEA (35 μL, 0.74 mmol). The reaction mixture was warmed to r.t., stirred for 12 h, diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were washed with 10% HCl (2x) and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (4:1, CH_2Cl_2/acetone containing 1% Et_3N) to afford **415** (62 mg, 70%) as a colorless solid: $[\alpha]_D$ -54.6 (*c* 0.35, $CHCl_3$); IR (KBr) 3304, 3062, 3030, 2938, 1715, 1651, 1623, 1533, 1454, 1239 cm^{-1}; ^1H NMR (DMSO-d_6, 8:1 mixture of amide bond rotamers) δ 8.31 (t, *J* = 5.7 Hz, 1 H), 8.27 (d, *J* = 8.6 Hz, 1 H), 8.05 (d, *J* = 8.9 Hz, 1 H), 7.88 (q, *J* = 4.6 Hz, 1 H), 7.33-7.16 (m, 15 H), 5.08 (d, *J* = 12.6 Hz, 1 H), 4.95 (d, *J* = 12.6 Hz, 1 H), 4.32 (t, *J* = 8.4 Hz, 1 H), 4.23-4.17 (m, 2 H), 3.76 (dd, *J* = 16.9, 6.7 Hz, 1 H), 3.74-3.67 (m, 1 H), 3.57-3.50 (m, 2 H), 2.54 (d, *J* = 4.5 Hz, 3 H), 2.02-1.80 (m, 5 H), 1.60-1.48 (m, 3 H), 0.87-0.76 (m, 4 H); ^{13}C NMR (DMSO-d_6) δ 172.13, 171.81, 170.67, 167.97, 155.72, 142.62, 137.16, 128.35, 128.29, 128.18, 128.07, 127.82, 127.69, 127.00, 126.79, 126.51, 126.45, 65.32, 60.03, 57.02, 54.85, 47.11, 42.16, 29.26, 27.80, 25.69, 25.22, 24.36, 20.34, 18.87, 12.50, 11.97; MS

(ESI) *m/z* (intensity) 688 ([M+Na]$^+$, 100); HRMS (ESI) *m/z* calculated for $C_{38}H_{43}N_5O_6Na$ (M+Na) 688.3111, found 688.3109.



416

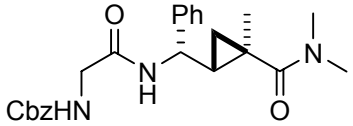
Cbz-*D*-$^{\alpha}$MeΔPhg-*L*-Pro-OMe (416). To a solution of (-)-**379** (45 mg, 0.13 mmol) in dry Et_2O (1.0 mL) were added two portions of KOTMS (66 mg, 0.51 mmol) over 4 h. The reaction mixture was stirred for 10 h, diluted with H_2O, acidified with 10% HCl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was dissolved in dry CH_2Cl_2 (1.0 mL) and treated with *L*-Pro-OMe•HCl (42 mg, 0.25 mmol), EDCI (29 mg, 0.15 mmol), DMAP (2.0 mg, 0.015 mmol) and DIPEA (0.11 mL, 0.64 mmol), stirred for 12 h, diluted with EtOAc and washed with 10% HCl, H_2O and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (1:4, hexanes/EtOAc containing 1% v/v Et_3N) to afford **416** (43 mg, 75%) as a colorless foam: $[\alpha]_D$ -105.6 (*c* 1.0, $CHCl_3$); IR (neat) 3315, 3058, 3027, 2954, 1739, 1715, 1624, 1526, 1425, 1244 cm^{-1}; ^{1}H NMR (8.0:1 mixture of rotamers) major rotamer δ 7.57-7.54 (m, 2 H), 7.38-7.29 (m, 8 H), 5.38 (bd, *J* = 7.2 Hz, 1 H), 5.12, 5.09 (AB, *J* = 12.2 Hz, 2 H), 4.48-4.40 (m, 1 H), 4.35 (dd, *J* = 8.5, 4.6 Hz, 1 H), 3.68 (s, 3 H), 3.47-3.38 (m, 1 H), 3.11 (bs, 1 H), 2.15-2.05 (m, 1 H), 1.85-1.77 (m, 2 H), 1.72-1.61 (m, 2 H), 1.43-1.33 (m, 1 H), 1.36 (s, 3 H), 0.85-0.79 (m, 1 H); minor rotamer (representative peaks) δ 4.23 (dd, *J* = 5.6, 3.4 Hz, 1 H); ^{13}C NMR δ 172.72, 172.46, 155.94, 142.06, 136.46, 128.66, 128.45, 128.04, 127.97, 127.55, 127.00, 66.81, 59.09, 55.35, 52.01, 46.81, 28.78, 27.86, 26.15, 24.96, 17.52, 15.27; MS (ESI) *m/z* (intensity) 473 ([M+Na]$^+$, 100), 451 ([M+H]$^+$, 5); HRMS (ESI) *m/z* calculated for $C_{26}H_{30}N_2O_5Na$ (M+Na) 473.2052, found 473.2049.



417

Cbz-*D*-$^{\alpha}$MeΔPhg-NMe$_2$ (417). To a solution of (-)-**379** (45 mg, 0.13 mmol) in dry Et_2O (1.0 mL) were added two portions of KOTMS (66 mg, 0.51 mmol) over 4 h. The reaction mixture was stirred for 10 h, diluted with H_2O, acidified with 10% HCl, and extracted with EtOAc (3x).

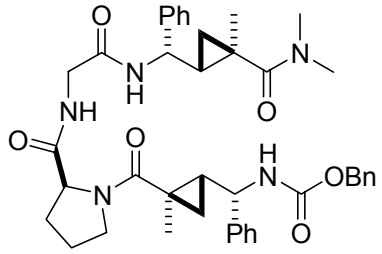
The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was dissolved in dry CH_2Cl_2 (1.0 mL) and treated with Me_2NH•HCl (52 mg, 0.64 mmol), EDCI (29 mg, 0.15 mmol), DMAP (2.0 mg, 0.015 mmol) and DIPEA (0.11 mL, 0.64 mmol), stirred for 12 h, diluted with EtOAc and washed with 10% HCl, H_2O and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (1:4, hexanes/EtOAc containing 1% v/v Et_3N) to afford **417** (33 mg, 70%) as a colorless foam: $[\alpha]_D$ -71.1 (*c* 0.71, $CHCl_3$); IR (neat) 3294, 3064, 3031, 2933, 1716, 1622, 1527, 1497, 1454, 1258, 1130 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63-7.60 (m, 2 H), 7.40-7.25 (m, 8 H), 5.29 (bd, *J* = 6.7 Hz, 1 H), 5.12, 5.10 (AB, *J* = 12.2 Hz, 2 H), 4.46 (bt, *J* = 8.6 Hz, 1 H), 2.83 (s, 6 H), 1.71-1.62 (m, 1 H), 1.32 (s, 3 H), 1.22 (dd, *J* = 8.9, 5.0 Hz, 1 H), 0.90-0.84 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.69, 156.02, 141.87, 136.41, 128.66, 128.47, 128.04, 127.56, 127.08, 66.80, 55.20, 36.28 (b), 27.47, 25.58, 18.00, 16.16; MS (ESI) *m/z* (intensity) 389 ($[M+Na]^+$, 100); HRMS (ESI) *m/z* calculated for $C_{22}H_{26}N_2O_3Na$ (M+Na) 389.1841, found 389.1855.



418

Cbz-Gly-*D*-$^{\alpha}$MeΔPhg-NMe$_2$ (418). To a mixture of **417** (83 mg, 0.23 mmol) and Pd/C (24 mg, 0.023 mmol, 10 wt% Pd/C) was added under N_2 MeOH (2.0 mL). The flask was evacuated and purged with H_2 (1 atm), and the reaction mixture was stirred under an atmosphere of H_2 for 2 h, filtered through Celite and concentrated. The residue was dissolved in dry DMF (2.0 mL) and treated at 0 °C with Cbz-Gly-OH (95 mg, 0.45 mmol), BOP (0.12 g, 0.27 mmol) and DIPEA (79 μL, 0.45 mmol). The mixture was stirred for 30 min, warmed to r.t., stirred for 10 h, diluted with EtOAc, washed with H_2O (5x) and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (7:3, CH_2Cl_2/acetone containing 1% v/v Et_3N) to afford **418** (75 mg, 78%) as a colorless foam: $[\alpha]_D$ -68.9 (*c* 0.92, $CHCl_3$); IR (neat) 3416 cm^{-1}; ^1H NMR δ 7.60 (d, *J* = 7.4 Hz, 2 H), 7.36-7.21 (m, 8 H), 6.83 (bd, *J* = 7.3 Hz, 1 H), 5.53 (bs, 1 H), 5.14-5.06 (m, 2 H), 4.81-4.74 (m, 1 H), 3.96-3.82 (m, 2 H), 2.85 (s, 6 H), 1.70 (dt, *J* = 9.4, 6.4 Hz, 1 H), 1.30 (s, 3 H), 1.17-1.12 (m, 1 H), 0.82 (t, *J* = 5.5 Hz, 1 H); ^{13}C NMR δ 173.88, 168.19, 156.51, 141.27, 136.14, 128.68, 128.51, 128.19, 128.04, 127.59, 127.24, 67.14, 53.03, 44.61, 36.48 (b), 26.92, 25.59, 18.13, 16.10; MS (ESI) *m/z* (intensity) 446 ($[M+Na]^+$, 100), 424

([M+H]$^+$, 13); HRMS (ESI) *m/z* calculated for $C_{24}H_{29}N_3O_4Na$ (M+Na) 446.2056, found 446.2064.



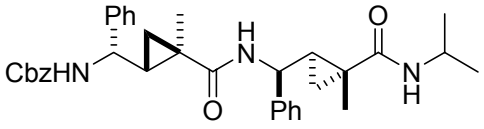
421

Cbz-*D*-$^{\alpha}$MeΔPhg-*L*-Pro-Gly-*D*-$^{\alpha}$MeΔPhg-NMe$_2$ (421). Saponification of **417**: To a solution of **417** (64 mg, 0.14 mmol) in dry Et_2O (1.5 mL) was added KOTMS (37 mg, 0.28 mmol). The reaction mixture was stirred for 4 h, acidified with 10% HCl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated.

N-Cbz Deprotection of **418**: To a mixture of **418** (75 mg, 0.18 mmol) and Pd/C (19 mg, 0.018 mmol, 10 wt% Pd) was added under N_2 MeOH (2 mL). The flask was evacuated, purged with H_2 (1 atm) and the mixture was stirred under an atmosphere of H_2 for 1.5 h, filtered through Celite and concentrated.

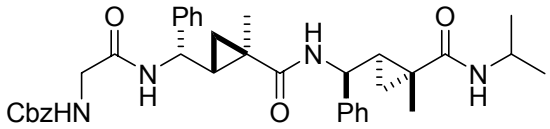
Fragment coupling: The amine and acid were concentrated into a 25 mL flask and the residue was dissolved in dry CH_2Cl_2 (1.5 mL) and treated with EDCI (33 mg, 0.17 mmol) and DMAP (2.0 mg, 0.018 mmol). The reaction mixture was stirred for 12 h, diluted with EtOAc, washed with H_2O (2x) and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (3:2, CH_2Cl_2/acetone containing 1% v/v Et_3N) to give **421** (51 mg, 56%) as a colorless solid. The solid was further purified by reverse phase HPLC (55:45, CH_3CN/H_2O, Rainin 10 mm x 25 cm C18 column) to afford **421** (33 mg) as a colorless solid: $[\alpha]_D$ -21.5 (*c* 0.40, $CHCl_3$); IR (KBr) 3326, 3061, 2927, 1718, 1686, 1670, 1655, 1620, 1527, 1243 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.40-8.38 (m, 1 H), 8.07 (d, *J* = 8.7 Hz, 1 H), 7.74 (d, *J* = 8.9 Hz, 1 H), 7.58 (d, *J* = 7.5 Hz, 2 H), 7.51 (d, *J* = 7.4 Hz, 2 H), 7.37-7.23 (m, 11 H), 5.04-4.99 (m, 2 H), 4.56 (app t, *J* = 10.1 Hz, 1 H), 4.25 (t, *J* = 9.9 Hz, 1 H), 4.11 (app t, *J* = 6.3 Hz, 1 H), 3.77 (dd, *J* = 17.0, 6.9 Hz, 1 H), 3.48 (dd, *J* = 16.9, 5.0 Hz, 1 H), 3.42-3.38 (m, 1 H), 3.18-3.17 (m, 1 H), 2.37 (bs, 6 H), 2.03-1.97 (m, 1 H), 1.85-1.81 (m, 1 H), 1.73-1.67 (m, 2 H), 1.65-1.62 (m, 1 H), 1.54-1.49 (m, 1 H), 1.20 (s, 3 H), 1.19 (s, 3 H), 1.10 (dd, *J* = 8.6, 4.4 Hz, 1 H), 0.99 (dd, *J* = 9.0, 4.7 Hz, 1 H), 0.59 (bt, 1 H), 0.40 (bt, 1 H); ^{13}C NMR (151 MHz, DMSO-

d_6) δ 172.73, 172.27, 172.25, 167.54, 155.77, 142.99, 142.80, 137.05, 128.36, 128.28, 128.17, 127.73, 127.65, 127.08, 126.99, 126.87, 65.37, 60.38, 54.46, 52.27, 47.09, 42.22, 28.68, 27.48, 26.29, 25.42, 25.10, 24.75, 17.39, 17.29, 15.73, 14.79; MS (ESI) *m/z* (intensity) 730 ($[M+Na]^+$, 100), 708 ($[M+H]^+$, 9); HRMS (ESI) *m/z* calculated for $C_{41}H_{49}N_5O_6Na$ (M+Na) 730.3581, found 730.3592.



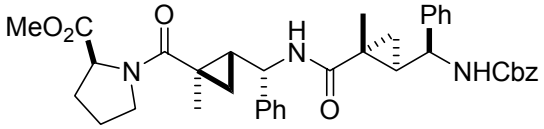
422

Cbz-*D*-$^{\alpha}$MeΔPhg-*D*-$^{\alpha}$MeΔPhg-NHPr^{i} (422). To a solution of (-)-**393** (34 mg, 0.063 mmol) in MeOH (0.50 mL) was added NaOH (0.50 mL, 2.0 M in H_2O) and THF (0.20 mL). The reaction mixture was stirred for 2 h, acidified with 10% HCl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was dissolved in dry DMF (1.0 mL) and treated at 0 °C with *i*-$PrNH_2$•HCl (18 mg, 0.19 mmol), BOP (33 mg, 0.076 mmol) and DIPEA (16 μL, 0.094 mmol). The mixture was stirred for 30 min, warmed to r.t., stirred for 10 h, diluted with EtOAc, washed with H_2O (5x) and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (3:7, hexanes/EtOAc containing 1% v/v Et_3N) to afford **422** (24 mg, 67%) as a colorless foam: $[\alpha]_D$ -82.4 (*c* 0.85, $CHCl_3$); IR (neat) 3316, 3031, 2971, 1705, 1630, 1522, 1456, 1258, 1205 cm^{-1}; ^1H NMR δ 7.37-7.24 (m, 15 H), 6.23 (d, *J* = 8.2 Hz, 1 H), 5.48 (d, *J* = 8.0 Hz, 1 H), 5.43 (d, *J* = 8.0 Hz, 1 H), 5.16-5.07 (m, 2 H), 4.89-4.83 (m, 1 H), 4.52 (bt, *J* = 9.6 Hz, 1 H), 4.06 (app. sextet, *J* = 6.6 Hz, 1 H), 1.99-1.88 (m, 2 H), 1.55 (dd, *J* = 8.9, 4.2 Hz, 1 H), 1.40 (dd, *J* = 9.0, 3.9 Hz, 1 H), 1.27 (s, 3 H), 1.25 (s, 3 H), 1.14 (d, *J* = 6.5 Hz, 3 H), 1.13 (d, *J* = 6.5 Hz, 3 H), 0.95-0.87 (m, 1 H), 0.70 (dd, *J* = 6.2, 4.2 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.58, 173.14, 155.99, 141.71, 136.38, 128.77, 128.68, 128.52, 128.13, 128.04, 127.79, 127.50, 126.71, 126.60, 66.91, 54.86, 52.67, 41.71, 30.82, 30.14, 24.21, 24.02, 22.85, 22.79, 20.28, 19.72, 14.67; MS (ESI) 590 ($[M+Na]^+$, 48), 568 ($[M+H]^+$, 51), 547 (80), 359 (100); HRMS (ESI) m/z calculated for $C_{35}H_{42}N_3O_4$ (M+H) 568.3175, found 568.3182.



423

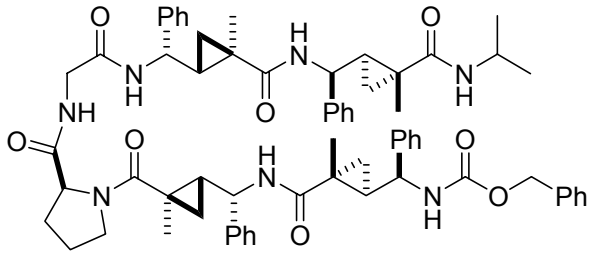
Cbz-Gly-*D*-$^{\alpha}$MeΔPhg-*D*-$^{\alpha}$MeΔPhg-NHPr^{i} (423). To a mixture of **422** (24 mg, 0.042 mmol) and Pd/C (5.0 mg, 0.0042 mmol, 10 wt% Pd/C) was added under N_2 MeOH (1.0 mL). The flask was evacuated and purged with H_2 (1 atm), and the reaction mixture was stirred under an atmosphere of H_2 for 2 h, filtered through Celite and concentrated. The residue was dissolved in dry DMF (1.0 mL), treated at 0 °C with BOP (47 mg, 0.11 mmol), Cbz-Gly-OH (22 mg, 0.11 mmol) and DIPEA (18 μL, 0.11 mmol), stirred for 30 min, warmed to r.t., and stirred for 10 h. The solution was diluted with EtOAc, washed with H_2O (5x) and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (4:1, CH_2Cl_2/acetone containing 1% v/v Et_3N) to give **423** (24 mg, 92%) as a colorless foam: $[\alpha]_D$ -81.6 (*c* 0.81, $CHCl_3$); IR (neat) 3313, 3031, 2971, 1717, 1628, 1521, 1456, 1255 cm^{-1}; ^1H NMR δ 7.33-7.18 (m, 16 H), 6.44 (d, *J* = 8.7 Hz, 1 H), 5.56 (bs, 1 H), 5.50 (d, *J* = 8.1 Hz, 1 H), 5.13-5.04 (m, 2 H), 4.86-4.77 (m, 2 H), 4.16-3.94 (m, 1 H), 3.88-3.84 (m, 1 H), 1.98-1.88 (m, 2 H), 1.47 (dd, *J* = 8.9, 4.1 Hz, 1 H), 1.37 (dd, *J* = 9.1, 4.0 Hz, 1 H), 1.23 (s, 3 H), 1.21 (s, 3 H), 1.14 (d, *J* = 6.5 Hz, 3 H), 1.11 (d, *J* = 6.5 Hz, 3 H), 0.77 (dd, *J* = 6.2, 4.5 Hz, 1 H), 0.62 (dd, *J* = 6.4, 4.1 Hz, 1 H); ^{13}C NMR δ 173.78, 173.14, 168.08, 156.37, 141.62, 141.41, 136.17, 128.68, 128.62, 128.59, 128.48, 128.14, 128.02, 127.66, 127.44, 126.68, 67.03, 52.71, 52.47, 44.43, 41.71, 30.51, 30.18, 24.13, 22.76, 20.31, 19.62, 14.63, 14.53; MS (EI) *m/z* (intensity) 624 (M^+, 26), 516 (20), 389 (15), 327 (30), 245 (43), 230 (47), 140 (91), 91 (100); HRMS (EI) *m/z* calculated for $C_{37}H_{44}N_4O_5$ 624.3312, found 624.3326.



425

Cbz-*D*-$^{\alpha}$MeΔPhg-*D*-$^{\alpha}$MeΔPhg-*L*-Pro-OMe (425). To a solution of (-)-**393** (27 mg, 0.050 mmol) in MeOH (0.50 mL) was added NaOH (0.50 mL, 2.0 M in H_2O) and THF (0.20 mL). The reaction mixture was stirred for 2 h, acidified with 10% HCl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was dissolved in dry DMF (1.0 mL), treated at 0 °C with *L*-Pro-OMe•HCl (12 mg, 0.075

mmol), BOP (26 mg, 0.060 mmol) and DIPEA (17 μL, 0.10 mmol), stirred for 30 min, warmed to r.t., stirred for 10 h, diluted with EtOAc and washed with H_2O (5x) and brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (3:7, hexanes/EtOAc containing 1% v/v Et_3N) to afford **425** (23 mg, 72%) as a colorless foam: $[\alpha]_D$ -112.0 (*c* 0.69, $CHCl_3$); IR (neat) 3319, 3030, 2952, 1743, 1714, 1628, 1522, 1453, 1426, 1256, 1196, 1175 cm^{-1}; ^1H NMR δ 7.56 (d, *J* = 7.3 Hz, 2 H), 7.36-7.23 (m, 13 H), 6.10 (bd, *J* = 8.2 Hz, 1 H), 5.38 (d, *J* = 8.2 Hz, 1 H), 5.12, 5.11 (AB, J = 12.2 Hz, 2 H), 4.80 (t, *J* = 9.9 Hz, 1 H), 4.52 (bt, *J* = 9.7 Hz, 1 H), 4.21 (dd, *J* = 8.7, 4.5 Hz, 1 H), 3.71 (s, 3 H), 3.56-3.46 (m, 1 H), 3.29-3.21 (m, 1 H), 2.19-2.09 (m, 1 H), 1.99-1.85 (m, 3 H), 1.83-1.67 (m, 2 H), 1.54 (dd, *J* = 9.0, 4.2 Hz, 1 H), 1.32 (s, 3 H), 1.27 (s, 3 H), 1.32-1.21 (m, 1 H), 0.89-0.87 (m, 1 H), 0.74 (t, *J* = 5.3 Hz, 1 H); ^{13}C NMR δ 173.53, 172.78, 172.58, 155.98, 141.81, 141.74, 136.36, 128.69, 128.48, 128.09, 128.03, 127.67, 127.47, 127.11, 126.60, 66.86, 59.08, 54.87, 52.86, 52.11, 46.92, 30.65, 28.82, 27.34, 26.24, 24.95, 23.99, 20.31, 17.07, 15.10, 14.71; MS (EI) *m/z* (intensity) 637 (M^+, 2), 529 (2), 294 (19), 201 (57), 145 (58), 91 (100); HRMS (ESI) *m/z* calculated for $C_{38}H_{43}N_3O_6$ (M+H) 637.3152, found 637.3126.



426

Cbz-*D*-$^{\alpha}$MeΔPhg-*D*-$^{\alpha}$MeΔPhg-*L*-Pro-Gly-*D*-$^{\alpha}$MeΔPhg-*D*-$^{\alpha}$MeΔPhg-NHPr^{i} (426).

Saponification of **425**: To a solution of **425** (20 mg, 0.031 mmol) in MeOH (0.50 mL) was added NaOH (0.50 mL, 2.0 M in H_2O) and THF (0.20 mL). The reaction mixture was stirred for 1.5 h, acidified with 10% HCl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated.

N-Cbz Deprotection of **423**: To a mixture of **423** (24 mg, 0.038 mmol) and Pd/C (4.0 mg, 0.0038 mmol) was added under N_2 MeOH (1.0 mL). The flask was evacuated and purged with H_2, and the mixture was stirred under an atmosphere of H_2 for 4 h, filtered through Celite and concentrated.

Fragment Coupling: The amine and acid were concentrated into a 25 mL flask and the residue was dissolved in dry DMF (1.0 mL), cooled to 0 °C, treated with BOP (21 mg, 0.047 mmol) and DIPEA (8.0 μL, 0.047 mmol), stirred for 30 min, warmed to r.t. and stirred for 24 h. The solution was diluted with EtOAc and washed with H_2O (3x) and brine, dried (Na_2SO_4) and concentrated. The residue was purified by chromatography on deactivated SiO_2 (3:2, CH_2Cl_2/acetone containing 1% v/v Et_3N) to afford **426** (24 mg, 70%) as a colorless solid: $[\alpha]_D$ -28.8 (*c* 0.25, $CHCl_3$); IR (KBr) 3418, 3062, 3031, 2926, 2854, 1701, 1632, 1522, 1455, 1257, 1197 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 8.48 (t, *J* = 5.9 Hz, 1 H), 8.18 (d, *J* = 8.9 Hz, 1 H), 8.15 (d, *J* = 8.9 Hz, 1 H), 8.11 (d, *J* = 9.0 Hz, 1 H), 7.93 (d, *J* = 8.9 Hz, 1 H), 7.50 (d, *J* = 7.4 Hz, 2 H), 7.38-7.30 (m, 12 H), 7.27-7.23 (m, 5 H), 7.19-7.10 (m, 6 H), 5.04-5.00 (m, 2 H), 4.78 (t, *J* = 9.9 Hz, 1 H), 4.69 (t, *J* = 9.8 Hz, 1 H), 4.40 (t, *J* = 9.6 Hz, 1 H), 4.17-4.11 (m, 2 H), 3.91-3.85 (m, 2 H), 3.61-3.55 (m, 2 H), 3.49-3.46 (m, 1 H), 2.06-2.03 (m, 1 H), 1.97-1.90 (m, 3 H), 1.79-1.73 (m, 3 H), 1.66-1.61 (m, 1 H), 1.28 (s, 3 H), 1.18-1.14 (m, 3 H), 1.12 (s, 3 H), 1.04 (d, *J* = 6.3 Hz, 3 H), 1.03 (d, *J* = 6.0 Hz, 3 H), 0.99 (s, 3 H), 0.93 (s, 3 H), 0.88-0.86 (m, 1 H), 0.56 (bs, 1 H), 0.40-0.38 (bm, 2 H), -0.34--0.32 (bm, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.96, 172.74, 172.54, 172.44, 172.42, 168.10, 155.83, 142.94, 142.82, 142.63, 142.56, 137.09, 128.31, 128.17, 128.03, 127.91, 127.76, 127.71, 127.07, 126.92, 126.90, 126.60, 126.49, 126.34, 126.16, 65.34, 60.40, 54.01, 51.89, 51.28, 50.44, 47.24, 42.20, 40.72, 30.73, 29.84, 29.79, 28.73, 25.38, 24.97, 24.74, 24.42, 24.22, 23.91, 22.24, 22.15, 19.47, 19.12, 17.81, 16.98, 14.83, 14.81, 14.73, 14.33; MS (ESI) *m/z* (intensity) 1118 ($[M+Na]^+$, 100); HRMS (ESI) *m/z* calculated for $C_{66}H_{77}N_7O_8Na$ (M+Na) 1118.5731, found 1118.5764.

Appendix A

X-ray crystal data for 197

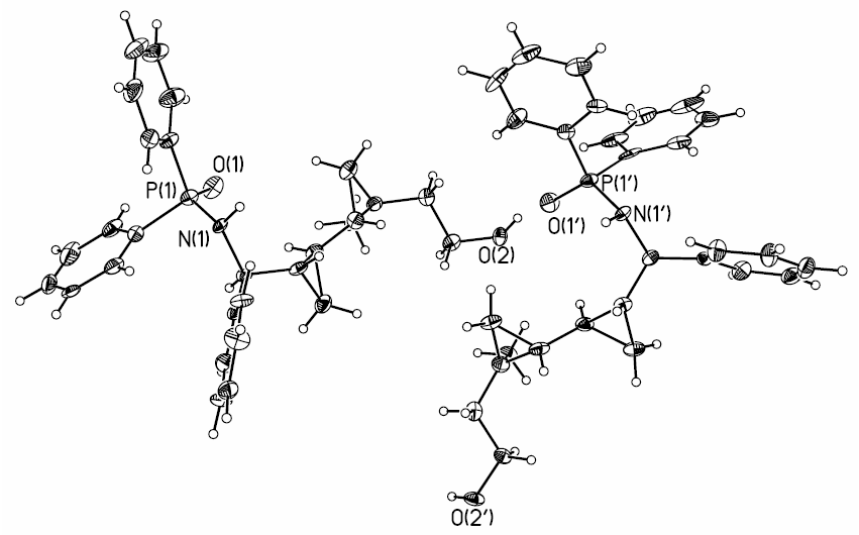


Table A1. Crystal data and structure refinement for corey1.

Identification code	corey1	
Empirical formula	$C_{28}H_{32}NO_2P$	
Formula weight	445.52	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pna2(1)	
Unit cell dimensions	a = 21.1797(19) Å	α= 90°.
	b = 7.0411(6) Å	β= 90°.
	c = 33.876(3) Å	γ = 90°.
Volume	5051.8(8) $Å^3$	
Z	8	
Density (calculated)	1.172 Mg/m^3	
Absorption coefficient	0.132 mm^{-1}	
F(000)	1904	
Crystal size	0.38 x 0.11 x 0.02 mm^3	
Theta range for data collection	1.92 to 25.00°.	
Index ranges	-25<=h<=25, -8<=k<=8, -40<=l<=40	
Reflections collected	38165	
Independent reflections	8914 [R(int) = 0.1610]	
Completeness to theta = 25.00°	100.0 %	
Max. and min. transmission	0.9974 and 0.9514	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8914 / 1 / 593	
Goodness-of-fit on F^2	0.959	
Final R indices [I>2sigma(I)]	R1 = 0.0755, wR2 = 0.1415	
R indices (all data)	R1 = 0.1426, wR2 = 0.1616	
Absolute structure parameter	0.51(16)	
Largest diff. peak and hole	0.369 and -0.331 $e.Å^{-3}$	

Table A2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for corey1. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)		x	y	z	U(eq)
P(1')	1976(1)	8471(2)	3238(1)	27(1)	C(13')	3469(3)	6468(9)	4562(2)	32(2)
P(1)	-501(1)	3705(2)	5905(1)	27(1)	C(13)	957(3)	2442(8)	4539(2)	30(2)
N(1')	2459(2)	10266(6)	3278(2)	22(1)	C(14')	3573(3)	4619(8)	4355(2)	37(2)
O(1)	-401(2)	2086(6)	5630(2)	44(1)	C(14)	1070(3)	436(8)	4682(2)	36(2)
N(1)	-37(2)	5551(6)	5889(2)	21(1)	C(15')	3768(3)	6601(9)	4970(2)	33(2)
O(1')	2026(2)	6850(6)	3506(2)	42(1)	C(15)	1251(3)	2933(8)	4144(2)	30(2)
C(1')	3444(3)	11557(8)	2985(2)	23(2)	C(16')	4485(3)	6609(8)	4961(2)	28(2)
C(1)	936(3)	6802(8)	6204(2)	25(2)	C(16)	1971(3)	2835(8)	4156(2)	33(2)
O(2)	2248(2)	3364(6)	3792(1)	32(1)	C(17')	1216(3)	9603(8)	3290(2)	28(1)
O(2')	4748(2)	6437(6)	5346(1)	35(1)	C(17)	-1276(3)	4745(8)	5839(2)	31(2)
C(2')	3286(3)	13416(9)	3025(2)	37(2)	C(18')	769(3)	8744(9)	3524(2)	42(2)
C(2)	772(3)	8715(9)	6179(2)	32(2)	C(18)	-1706(3)	3829(10)	5595(2)	55(2)
C(3')	3590(3)	14789(9)	2794(2)	38(2)	C(19)	-2305(3)	4561(11)	5548(3)	61(2)
C(3)	1062(3)	10022(9)	6412(2)	44(2)	C(19')	177(3)	9649(11)	3571(2)	51(2)
C(4')	4044(3)	14278(9)	2531(2)	40(2)	C(20)	-2469(4)	6194(12)	5729(3)	59(2)
C(4)	1542(3)	9541(10)	6661(2)	39(2)	C(20')	53(3)	11316(12)	3387(2)	55(2)
C(5')	4211(4)	12382(10)	2490(3)	39(2)	C(21')	497(4)	12178(9)	3142(3)	45(2)
C(5)	1706(4)	7670(10)	6691(3)	42(2)	C(21)	-2056(4)	7115(11)	5963(3)	52(2)
C(6)	1426(3)	6305(9)	6467(2)	39(2)	C(22')	1074(3)	11307(9)	3099(2)	31(2)
C(6')	3903(3)	11044(9)	2713(2)	36(2)	C(22)	-1445(3)	6402(10)	6027(2)	39(2)
C(7')	3160(2)	10029(8)	3247(2)	25(1)	C(23)	-457(3)	2880(8)	6407(2)	26(2)
C(7)	666(2)	5340(8)	5926(2)	25(1)	C(23')	2039(3)	7693(8)	2748(3)	36(2)
C(8')	3450(3)	10082(8)	3656(2)	26(1)	C(24')	2206(3)	8900(10)	2430(2)	41(2)
C(8)	977(3)	5471(8)	5530(2)	28(1)	C(24)	-637(3)	992(9)	6487(2)	41(2)
C(9')	4097(3)	9178(8)	3697(2)	38(2)	C(25)	-636(4)	381(12)	6878(3)	62(3)
C(9)	1597(3)	4433(9)	5464(2)	38(2)	C(25')	2202(4)	8251(13)	2047(3)	54(2)
C(10')	3526(3)	8268(8)	3886(2)	31(2)	C(26)	-475(4)	1487(13)	7181(3)	53(2)
C(10)	996(3)	3759(9)	5267(2)	33(2)	C(26')	2016(4)	6381(15)	1961(3)	73(4)
C(11')	3445(3)	8265(8)	4325(2)	33(2)	C(27)	-295(3)	3333(12)	7106(2)	48(2)
C(11)	929(3)	4063(8)	4843(2)	32(2)	C(27')	1864(4)	5202(13)	2262(3)	60(2)
C(12)	340(3)	3410(10)	4634(2)	43(2)	C(28)	-289(3)	4033(9)	6727(2)	38(2)
C(12')	2854(3)	7474(8)	4507(2)	37(2)	C(28')	1879(3)	5832(9)	2643(2)	47(2)

Table A3. Bond lengths [Å] and angles [°] for corey1.

P(1')-O(1')	1.462(5)	C(26')-C(27')	1.355(12)	C(13)-C(12)-H(12B)	117.6
P(1')-N(1')	1.633(5)	C(26')-H(26B)	0.95	H(12A)-C(12)-H(12B)	114.7
P(1')-C(23')	1.753(9)	C(27)-C(28)	1.374(10)	C(13')-C(12')-C(11')	60.1(4)
P(1')-C(17')	1.804(6)	C(27)-H(27A)	0.95	C(13')-C(12')-H(12C)	117.8
P(1)-O(1)	1.488(5)	C(27')-C(28')	1.364(11)	C(11')-C(12')-H(12C)	117.8
P(1)-N(1)	1.630(4)	C(27')-H(27B)	0.95	C(13')-C(12')-H(12D)	117.8
P(1)-C(23)	1.798(7)	C(28)-H(28A)	0.95	C(11')-C(12')-H(12D)	117.8
P(1)-C(17)	1.811(6)	C(28')-H(28B)	0.95	H(12C)-C(12')-H(12D)	114.9
N(1')-C(7')	1.497(6)	O(1')-P(1')-N(1')	120.4(3)	C(12')-C(13')-C(14')	118.8(6)
N(1')-H(1N')	0.99(6)	O(1')-P(1')-C(23')	109.8(3)	C(12')-C(13')-C(11')	60.3(4)
N(1)-C(7)	1.501(6)	N(1')-P(1')-C(23')	105.8(3)	C(14')-C(13')-C(11')	119.2(6)
N(1)-H(1)	0.86(5)	O(1')-P(1')-C(17')	110.5(3)	C(12')-C(13')-C(15')	116.6(5)
C(1')-C(2')	1.358(8)	N(1')-P(1')-C(17')	102.1(2)	C(14')-C(13')-C(15')	114.7(5)
C(1')-C(6')	1.386(8)	C(23')-P(1')-C(17')	107.4(3)	C(11')-C(13')-C(15')	116.7(5)
C(1')-C(7')	1.520(8)	O(1)-P(1)-N(1)	120.2(3)	C(12)-C(13)-C(15)	116.3(5)
C(1)-C(2)	1.394(8)	O(1)-P(1)-C(23)	109.7(3)	C(12)-C(13)-C(14)	119.4(6)
C(1)-C(6)	1.413(9)	N(1)-P(1)-C(23)	105.0(3)	C(15)-C(13)-C(14)	115.6(5)
C(1)-C(7)	1.508(8)	O(1)-P(1)-C(17)	111.1(3)	C(12)-C(13)-C(11)	59.2(4)
O(2)-C(16)	1.415(8)	N(1)-P(1)-C(17)	102.7(3)	C(15)-C(13)-C(11)	115.9(5)
O(2)-H(2)	0.80(8)	C(23)-P(1)-C(17)	107.1(3)	C(14)-C(13)-C(11)	118.9(5)
O(2')-C(16')	1.423(7)	C(7')-N(1')-P(1')	122.0(4)	C(13')-C(14')-H(14A)	109.5
O(2')-H(2')	1.05(8)	C(7')-N(1')-H(1N')	108(3)	C(13')-C(14')-H(14B)	109.5
C(2')-C(3')	1.400(9)	P(1')-N(1')-H(1N')	114(3)	H(14A)-C(14')-H(14B)	109.5
C(2')-H(2'A)	0.95	C(7)-N(1)-P(1)	121.1(4)	C(13')-C(14')-H(14C)	109.5
C(2)-C(3)	1.359(9)	C(7)-N(1)-H(1)	111(3)	H(14A)-C(14')-H(14C)	109.5
C(2)-H(2A)	0.95	P(1)-N(1)-H(1)	115(3)	H(14B)-C(14')-H(14C)	109.5
C(3')-C(4')	1.361(9)	C(2')-C(1')-C(6')	119.4(6)	C(13)-C(14)-H(14D)	109.5
C(3')-H(3'A)	0.95	C(2')-C(1')-C(7')	121.7(5)	C(13)-C(14)-H(14E)	109.5
C(3)-C(4)	1.363(9)	C(6')-C(1')-C(7')	118.8(5)	H(14D)-C(14)-H(14E)	109.5
C(3)-H(3A)	0.95	C(2)-C(1)-C(6)	117.4(6)	C(13)-C(14)-H(14F)	109.5
C(4')-C(5')	1.388(9)	C(2)-C(1)-C(7)	121.9(5)	H(14D)-C(14)-H(14F)	109.5
C(4')-H(4'A)	0.95	C(6)-C(1)-C(7)	120.2(5)	H(14E)-C(14)-H(14F)	109.5
C(4)-C(5)	1.366(9)	C(16)-O(2)-H(2)	132(6)	C(16')-C(15')-C(13')	113.5(5)
C(4)-H(4A)	0.95	C(16')-O(2')-H(2')	106(4)	C(16')-C(15')-H(15A)	108.9
C(5')-C(6')	1.372(10)	C(1')-C(2')-C(3')	119.8(6)	C(13')-C(15')-H(15A)	108.9
C(5')-H(5'A)	0.95	C(1')-C(2')-H(2'A)	120.1	C(16')-C(15')-H(15B)	108.9
C(5)-C(6)	1.361(10)	C(3')-C(2')-H(2'A)	120.1	C(13')-C(15')-H(15B)	108.9
C(5)-H(5A)	0.95	C(3)-C(2)-C(1)	120.4(6)	H(15A)-C(15')-H(15B)	107.7
C(6)-H(6A)	0.95	C(3)-C(2)-H(2A)	119.8	C(13)-C(15)-C(16)	112.2(5)
C(6')-H(6'A)	0.95	C(1)-C(2)-H(2A)	119.8	C(13)-C(15)-H(15C)	109.2
C(7')-C(8')	1.515(8)	C(4')-C(3')-C(2')	120.5(6)	C(16)-C(15)-H(15C)	109.2
C(7')-H(7'A)	1	C(4')-C(3')-H(3'A)	119.7	C(13)-C(15)-H(15D)	109.2
C(7)-C(8)	1.494(8)	C(2')-C(3')-H(3'A)	119.7	C(16)-C(15)-H(15D)	109.2
C(7)-H(7A)	1	C(2)-C(3)-C(4)	121.9(6)	H(15C)-C(15)-H(15D)	107.9
C(8')-C(10')	1.506(8)	C(2)-C(3)-H(3A)	119.1	O(2')-C(16')-C(15')	111.9(5)
C(8')-C(9')	1.517(7)	C(4)-C(3)-H(3A)	119.1	O(2')-C(16')-H(16A)	109.2
C(8')-H(8'A)	1	C(3')-C(4')-C(5')	119.9(7)	C(15')-C(16')-H(16A)	109.2
C(8)-C(10)	1.501(8)	C(3')-C(4')-H(4'A)	120	O(2')-C(16')-H(16B)	109.2
C(8)-C(9)	1.520(8)	C(5')-C(4')-H(4'A)	120	C(15')-C(16')-H(16B)	109.2
C(8)-H(8A)	1	C(3)-C(4)-C(5)	118.3(7)	H(16A)-C(16')-H(16B)	107.9
C(9')-C(10')	1.511(8)	C(3)-C(4)-H(4A)	120.8	O(2)-C(16)-C(15)	112.4(6)
C(9')-H(9'A)	0.99	C(5)-C(4)-H(4A)	120.8	O(2)-C(16)-H(16C)	109.1
C(9')-H(9'B)	0.99	C(6')-C(5')-C(4')	119.0(7)	C(15)-C(16)-H(16C)	109.1
C(9)-C(10)	1.515(8)	C(6')-C(5')-H(5'A)	120.5	O(2)-C(16)-H(16D)	109.1

Table A3. Cont'd

C(9)-H(9A)	0.99	C(4')-C(5')-H(5'A)	120.5	C(15)-C(16)-H(16D)	109.1
C(9)-H(9B)	0.99	C(6)-C(5)-C(4)	122.0(7)	H(16C)-C(16)-H(16D)	107.9
C(10')-C(11')	1.495(9)	C(6)-C(5)-H(5A)	119	C(18')-C(17')-C(22')	119.8(6)
C(10')-H(10A)	1	C(4)-C(5)-H(5A)	119	C(18')-C(17')-P(1')	118.4(5)
C(10)-C(11)	1.460(8)	C(5)-C(6)-C(1)	119.8(7)	C(22')-C(17')-P(1')	121.7(5)
C(10)-H(10B)	1	C(5)-C(6)-H(6A)	120.1	C(22)-C(17)-C(18)	119.8(6)
C(11')-C(13')	1.500(9)	C(1)-C(6)-H(6A)	120.1	C(22)-C(17)-P(1)	121.4(5)
C(11')-C(12')	1.503(9)	C(5')-C(6')-C(1')	121.3(6)	C(18)-C(17)-P(1)	118.8(5)
C(11')-H(11A)	1	C(5')-C(6')-H(6'A)	119.4	C(17')-C(18')-C(19')	118.5(6)
C(11)-C(12)	1.505(9)	C(1')-C(6')-H(6'A)	119.4	C(17')-C(18')-H(18A)	120.8
C(11)-C(13)	1.538(8)	N(1')-C(7')-C(8')	109.6(5)	C(19')-C(18')-H(18A)	120.8
C(11)-H(11B)	1	N(1')-C(7')-C(1')	110.8(5)	C(19)-C(18)-C(17)	120.0(7)
C(12)-C(13)	1.508(8)	C(8')-C(7')-C(1')	110.8(4)	C(19)-C(18)-H(18B)	120
C(12)-H(12A)	0.99	N(1')-C(7')-H(7'A)	108.5	C(17)-C(18)-H(18B)	120
C(12)-H(12B)	0.99	C(8')-C(7')-H(7'A)	108.5	C(20)-C(19)-C(18)	120.2(8)
C(12')-C(13')	1.494(9)	C(1')-C(7')-H(7'A)	108.5	C(20)-C(19)-H(19A)	119.9
C(12')-H(12C)	0.99	C(8)-C(7)-N(1)	110.8(5)	C(18)-C(19)-H(19A)	119.9
C(12')-H(12D)	0.99	C(8)-C(7)-C(1)	110.6(5)	C(20')-C(19')-C(18')	120.7(7)
C(13')-C(14')	1.496(8)	N(1)-C(7)-C(1)	111.1(4)	C(20')-C(19')-H(19B)	119.6
C(13')-C(15')	1.522(9)	C(8)-C(7)-H(7A)	108.1	C(18')-C(19')-H(19B)	119.6
C(13)-C(15)	1.515(9)	N(1)-C(7)-H(7A)	108.1	C(19)-C(20)-C(21)	120.7(7)
C(13)-C(14)	1.513(8)	C(1)-C(7)-H(7A)	108.1	C(19)-C(20)-H(20A)	119.7
C(14')-H(14A)	0.98	C(10')-C(8')-C(7')	119.8(5)	C(21)-C(20)-H(20A)	119.7
C(14')-H(14B)	0.98	C(10')-C(8')-C(9')	60.0(4)	C(19')-C(20')-C(21')	121.3(7)
C(14')-H(14C)	0.98	C(7')-C(8')-C(9')	116.2(5)	C(19')-C(20')-H(20B)	119.3
C(14)-H(14D)	0.98	C(10')-C(8')-H(8'A)	116.3	C(21')-C(20')-H(20B)	119.3
C(14)-H(14E)	0.98	C(7')-C(8')-H(8'A)	116.3	C(22')-C(21')-C(20')	118.0(7)
C(14)-H(14F)	0.98	C(9')-C(8')-H(8'A)	116.3	C(22')-C(21')-H(21A)	121
C(15')-C(16')	1.519(8)	C(7)-C(8)-C(10)	119.7(5)	C(20')-C(21')-H(21A)	121
C(15')-H(15A)	0.99	C(7)-C(8)-C(9)	118.9(5)	C(20)-C(21)-C(22)	121.1(7)
C(15')-H(15B)	0.99	C(10)-C(8)-C(9)	60.2(4)	C(20)-C(21)-H(21B)	119.4
C(15)-C(16)	1.527(9)	C(7)-C(8)-H(8A)	115.6	C(22)-C(21)-H(21B)	119.4
C(15)-H(15C)	0.99	C(10)-C(8)-H(8A)	115.6	C(21')-C(22')-C(17')	121.6(7)
C(15)-H(15D)	0.99	C(9)-C(8)-H(8A)	115.6	C(21')-C(22')-H(22A)	119.2
C(16')-H(16A)	0.99	C(10')-C(9')-C(8')	59.6(4)	C(17')-C(22')-H(22A)	119.2
C(16')-H(16B)	0.99	C(10')-C(9')-H(9'A)	117.8	C(17)-C(22)-C(21)	118.1(7)
C(16)-H(16C)	0.99	C(8')-C(9')-H(9'A)	117.8	C(17)-C(22)-H(22B)	120.9
C(16)-H(16D)	0.99	C(10')-C(9')-H(9'B)	117.8	C(21)-C(22)-H(22B)	120.9
C(17')-C(18')	1.375(8)	C(8')-C(9')-H(9'B)	117.8	C(28)-C(23)-C(24)	117.8(7)
C(17')-C(22')	1.397(8)	H(9'A)-C(9')-H(9'B)	114.9	C(28)-C(23)-P(1)	123.9(5)
C(17)-C(22)	1.376(8)	C(10)-C(9)-C(8)	59.3(4)	C(24)-C(23)-P(1)	118.2(5)
C(17)-C(18)	1.389(9)	C(10)-C(9)-H(9A)	117.8	C(28')-C(23')-C(24')	115.3(8)
C(18')-C(19')	1.414(9)	C(8)-C(9)-H(9A)	117.8	C(28')-C(23')-P(1')	121.0(7)
C(18')-H(18A)	0.95	C(10)-C(9)-H(9B)	117.8	C(24')-C(23')-P(1')	123.5(5)
C(18)-C(19)	1.378(10)	C(8)-C(9)-H(9B)	117.8	C(25')-C(24')-C(23')	121.1(7)
C(18)-H(18B)	0.95	H(9A)-C(9)-H(9B)	115	C(25')-C(24')-H(24A)	119.5
C(19)-C(20)	1.349(11)	C(11')-C(10')-C(8')	120.3(5)	C(23')-C(24')-H(24A)	119.5
C(19)-H(19A)	0.95	C(11')-C(10')-C(9')	120.9(5)	C(25)-C(24)-C(23)	118.3(8)
C(19')-C(20')	1.355(10)	C(8')-C(10')-C(9')	60.4(4)	C(25)-C(24)-H(24B)	120.9
C(19')-H(19B)	0.95	C(11')-C(10')-H(10A)	114.8	C(23)-C(24)-H(24B)	120.9
C(20)-C(21)	1.349(11)	C(8')-C(10')-H(10A)	114.8	C(26)-C(25)-C(24)	123.6(8)
C(20)-H(20A)	0.95	C(9')-C(10')-H(10A)	114.8	C(26)-C(25)-H(25A)	118.2
C(20')-C(21')	1.394(11)	C(11)-C(10)-C(8)	117.7(6)	C(24)-C(25)-H(25A)	118.2

Table A3. Cont'd

C(20')-H(20B)	0.95	C(11)-C(10)-C(9)	118.0(5)	C(24')-C(25')-C(26')	120.6(9)
C(21')-C(22')	1.375(9)	C(8)-C(10)-C(9)	60.5(4)	C(24')-C(25')-H(25B)	119.7
C(21')-H(21A)	0.95	C(11)-C(10)-H(10B)	116.3	C(26')-C(25')-H(25B)	119.7
C(21)-C(22)	1.405(10)	C(8)-C(10)-H(10B)	116.3	C(25)-C(26)-C(27)	118.6(8)
C(21)-H(21B)	0.95	C(9)-C(10)-H(10B)	116.3	C(25)-C(26)-H(26A)	120.7
C(22')-H(22A)	0.95	C(10')-C(11')-C(13')	122.0(5)	C(27)-C(26)-H(26A)	120.7
C(22)-H(22B)	0.95	C(10')-C(11')-C(12')	120.3(5)	C(27')-C(26')-C(25')	118.9(8)
C(23)-C(28)	1.402(10)	C(13')-C(11')-C(12')	59.7(4)	C(27')-C(26')-H(26B)	120.5
C(23)-C(24)	1.410(8)	C(10')-C(11')-H(11A)	114.6	C(25')-C(26')-H(26B)	120.5
C(23')-C(28')	1.400(8)	C(13')-C(11')-H(11A)	114.6	C(28)-C(27)-C(26)	120.9(8)
C(23')-C(24')	1.417(11)	C(12')-C(11')-H(11A)	114.6	C(28)-C(27)-H(27A)	119.5
C(24')-C(25')	1.375(10)	C(10)-C(11)-C(12)	119.8(6)	C(26)-C(27)-H(27A)	119.5
C(24')-H(24A)	0.95	C(10)-C(11)-C(13)	123.1(5)	C(26')-C(27')-C(28')	120.5(8)
C(24)-C(25)	1.393(11)	C(12)-C(11)-C(13)	59.4(4)	C(26')-C(27')-H(27B)	119.8
C(24)-H(24B)	0.95	C(10)-C(11)-H(11B)	114.5	C(28')-C(27')-H(27B)	119.8
C(25)-C(26)	1.333(12)	C(12)-C(11)-H(11B)	114.5	C(27)-C(28)-C(23)	120.9(7)
C(25)-H(25A)	0.95	C(13)-C(11)-H(11B)	114.5	C(27)-C(28)-H(28A)	119.6
C(25')-C(26')	1.405(11)	C(11)-C(12)-C(13)	61.4(4)	C(23)-C(28)-H(28A)	119.6
C(25')-H(25B)	0.95	C(11)-C(12)-H(12A)	117.6	C(27')-C(28')-C(23')	123.5(9)
C(26)-C(27)	1.379(11)	C(13)-C(12)-H(12A)	117.6	C(27')-C(28')-H(28B)	118.3
C(26)-H(26A)	0.95	C(11)-C(12)-H(12B)	117.6	C(23')-C(28')-H(28B)	118.3

Table A4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for corey1. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P(1')	21(1)	20(1)	41(1)	3(1)	-6(1)	-2(1)
P(1)	25(1)	17(1)	37(1)	-3(1)	-2(1)	-3(1)
N(1')	17(2)	14(2)	33(3)	-5(2)	2(2)	-2(2)
O(1)	43(3)	27(2)	62(4)	-11(2)	11(3)	-3(2)
N(1)	16(2)	15(2)	33(3)	4(2)	2(2)	-5(2)
O(1')	44(3)	24(2)	56(4)	12(2)	-4(3)	-2(2)
C(1')	22(4)	28(3)	18(3)	-3(3)	-2(3)	-2(3)
C(1)	17(4)	27(4)	30(4)	1(3)	2(3)	5(3)
O(2)	37(3)	25(2)	33(3)	1(2)	8(2)	-3(2)
O(2')	37(3)	28(3)	41(3)	9(2)	-19(2)	-2(2)
C(2')	36(4)	29(4)	45(4)	-1(3)	12(3)	10(3)
C(2)	22(4)	27(4)	47(4)	-7(3)	-13(3)	2(3)
C(3')	48(5)	23(3)	42(4)	-1(3)	8(4)	-6(3)
C(3)	57(5)	23(3)	52(5)	-7(3)	-9(4)	4(3)
C(4')	39(4)	39(4)	43(4)	1(3)	6(4)	-11(3)
C(4)	35(4)	42(4)	41(4)	-5(3)	-2(3)	-14(3)
C(5')	24(5)	50(5)	44(6)	-1(4)	0(4)	4(3)
C(5)	30(6)	58(5)	37(5)	-1(4)	-16(4)	0(3)
C(6)	43(5)	33(4)	40(4)	3(3)	-5(4)	-9(3)
C(6')	29(4)	34(4)	43(4)	-5(3)	6(3)	9(3)
C(7')	19(3)	24(3)	32(3)	-4(3)	3(3)	3(2)
C(7)	17(3)	29(3)	28(3)	-4(3)	1(3)	9(2)
C(8')	23(3)	17(3)	39(4)	0(3)	-5(3)	5(2)
C(8)	15(3)	28(3)	40(4)	-9(3)	-1(3)	3(3)
C(9')	22(4)	42(4)	49(4)	-1(3)	-8(3)	12(3)
C(9)	28(4)	48(4)	39(4)	-5(3)	9(3)	3(3)
C(10')	25(3)	29(4)	39(4)	7(3)	-9(3)	3(3)
C(10)	26(3)	34(4)	39(4)	-5(3)	3(3)	2(3)
C(11')	25(3)	27(3)	47(4)	-1(3)	-14(3)	-4(3)
C(11)	36(4)	29(4)	31(4)	-6(3)	1(3)	0(3)
C(12)	31(4)	47(4)	50(5)	-3(4)	10(3)	3(4)
C(12')	22(4)	41(4)	49(5)	-7(3)	-6(3)	3(3)
C(13')	33(4)	30(4)	32(4)	-2(3)	-3(3)	1(3)
C(13)	24(4)	35(4)	31(4)	-2(3)	0(3)	0(3)
C(14')	45(4)	27(4)	39(4)	1(3)	-8(3)	-3(3)
C(14)	32(4)	30(4)	44(4)	2(3)	13(3)	-11(3)
C(15')	37(4)	27(4)	36(4)	2(3)	5(3)	4(3)
C(15)	36(4)	24(3)	29(4)	-6(3)	3(3)	2(3)
C(16')	33(4)	22(3)	30(4)	3(3)	-6(3)	5(3)
C(16)	33(4)	23(3)	43(4)	-3(3)	-1(3)	-5(3)
C(17')	28(3)	21(3)	36(4)	1(3)	-5(3)	-1(3)
C(17)	20(3)	26(3)	46(4)	1(3)	-1(3)	-3(3)
C(18')	33(4)	30(4)	64(5)	-3(4)	6(4)	-7(3)
C(18)	38(5)	41(4)	87(6)	10(4)	-9(4)	-8(4)
C(19)	33(5)	56(5)	93(7)	27(5)	-16(5)	-24(4)
C(19')	24(4)	43(4)	85(6)	-20(4)	21(4)	-14(3)
C(20)	25(4)	59(5)	93(7)	32(5)	5(4)	2(4)
C(20')	23(4)	69(6)	74(6)	-41(5)	-3(4)	-3(4)
C(21')	34(5)	39(4)	61(6)	-14(4)	-6(4)	14(3)
C(21)	39(5)	59(5)	57(6)	5(4)	18(5)	16(4)
C(22')	24(3)	32(4)	37(4)	-3(3)	-10(3)	5(3)

Table A4. Cont'd

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(22)	35(4)	44(4)	39(4)	2(3)	3(3)	1(3)
C(23)	26(4)	18(3)	33(5)	3(3)	2(3)	5(3)
C(23')	7(4)	25(4)	75(7)	-4(4)	-11(4)	2(3)
C(24')	23(4)	46(5)	53(5)	-19(4)	-13(3)	4(3)
C(24)	22(4)	32(4)	69(6)	11(4)	4(4)	6(3)
C(25)	39(5)	62(6)	85(7)	44(6)	17(5)	23(4)
C(25')	32(5)	94(7)	35(5)	-18(5)	-5(4)	17(4)
C(26)	31(5)	84(7)	44(6)	34(5)	10(4)	11(5)
C(26')	23(5)	116(9)	79(8)	-82(7)	-9(5)	12(5)
C(27)	14(4)	83(6)	49(6)	26(5)	-7(4)	-8(4)
C(27')	31(5)	60(6)	88(7)	-40(6)	-7(5)	4(4)
C(28)	21(4)	40(4)	52(5)	8(4)	-2(3)	-1(3)
C(28')	25(4)	32(4)	83(6)	-25(4)	-18(4)	4(3)

Table A5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for corey1.

	x	y	z	U(eq)		x	y	z	U(eq)
H(1N')	2370(30)	11110(80)	3507(17)	35(17)	H(14C)	4027	4406	4321	55
H(1)	-130(20)	6370(60)	5708(14)	0(13)	H(14D)	875	271	4942	53
H(2)	2130(40)	4040(110)	3620(20)	80(30)	H(14E)	1525	205	4702	53
H(2')	4690(30)	5010(120)	5430(20)	90(30)	H(14F)	883	-466	4496	53
H(2'A)	2971	13783	3209	44	H(15A)	3619	7778	5100	40
H(2A)	455	9108	5998	39	H(15B)	3623	5512	5131	40
H(3'A)	3477	16088	2821	45	H(15C)	1120	4231	4067	36
H(3A)	927	11307	6401	53	H(15D)	1092	2041	3941	36
H(4'A)	4247	15219	2375	48	H(16A)	4635	5543	4795	34
H(4A)	1756	10484	6811	47	H(16B)	4634	7807	4839	34
H(5'A)	4534	12016	2311	47	H(16C)	2129	3687	4366	40
H(5A)	2025	7312	6873	50	H(16D)	2102	1523	4222	40
H(6A)	1561	5021	6487	47	H(18A)	855	7569	3651	51
H(6'A)	4005	9740	2680	43	H(18B)	-1588	2698	5462	66
H(7'A)	3250	8761	3126	30	H(19A)	-2603	3913	5387	73
H(7A)	756	4053	6037	30	H(19B)	-136	9081	3733	61
H(8'A)	3374	11260	3813	31	H(20A)	-2881	6701	5690	71
H(8A)	934	6721	5393	33	H(20B)	-345	11910	3426	66
H(9'A)	4281	8553	3462	45	H(21A)	404	13333	3009	54
H(9'B)	4407	9808	3872	45	H(21B)	-2180	8265	6088	62
H(9A)	1920	5058	5297	46	H(22A)	1384	11878	2934	37
H(9B)	1767	3663	5684	46	H(22B)	-1156	7046	6195	47
H(10A)	3368	7102	3749	37	H(24A)	2322	10179	2482	49
H(10B)	803	2570	5375	40	H(24B)	-757	158	6280	49
H(11A)	3621	9407	4461	40	H(25A)	-756	-893	6932	74
H(11B)	1101	5301	4746	38	H(25B)	2326	9074	1839	65
H(12A)	158	4263	4432	51	H(26A)	-485	1013	7444	64
H(12B)	26	2688	4790	51	H(26B)	1996	5951	1695	87
H(12C)	2674	8152	4737	45	H(27A)	-173	4132	7319	58
H(12D)	2539	6887	4329	45	H(27B)	1746	3926	2208	72
H(14A)	3367	4654	4096	55	H(28A)	-169	5316	6682	45
H(14B)	3392	3586	4512	55	H(28B)	1776	4962	2847	56

Appendix B

X-ray crystal data for 366

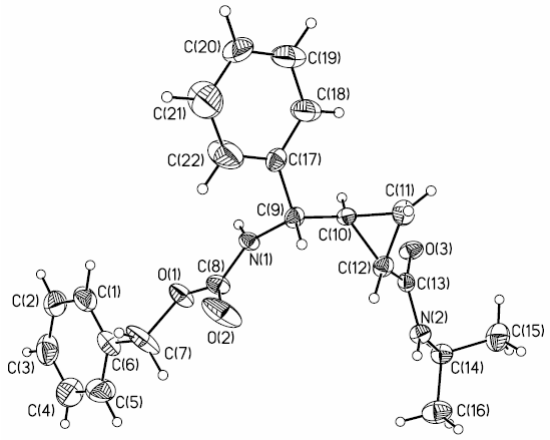


Table B1. Crystal data and structure refinement for corey6s.

Identification code	corey6s	
Empirical formula	$C_{22}H_{26}N_2O_3$	
Formula weight	366.45	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 12.8235(12) Å	α= 90°.
	b = 4.9657(5) Å	β= 95.861(2)°.
	c = 33.354(3) Å	γ = 90°.
Volume	2112.8(4) $Å^3$	
Z	4	
Density (calculated)	1.152 Mg/m^3	
Absorption coefficient	0.077 mm^{-1}	
F(000)	784	
Crystal size	0.21 x 0.09 x 0.08 mm^3	
Theta range for data collection	1.65 to 25.00°.	
Index ranges	-15<=h<=15, -5<=k<=5, -39<=l<=39	
Reflections collected	15845	
Independent reflections	3716 [R(int) = 0.0777]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	None	
Max. and min. transmission	0.9939 and 0.9840	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3716 / 0 / 253	
Goodness-of-fit on F^2	1.371	
Final R indices [I>2sigma(I)]	R1 = 0.0939, wR2 = 0.1838	
R indices (all data)	R1 = 0.1289, wR2 = 0.1949	
Extinction coefficient	0.0007(11)	
Largest diff. peak and hole	0.250 and -0.251 e.$Å^{-3}$	

Table B2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for corey6s. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	378(2)	479(5)	2126(1)	35(1)
N(1)	-404(2)	-898(6)	1542(1)	22(1)
C(1)	781(3)	-766(9)	2965(1)	46(1)
N(2)	2230(2)	-276(6)	523(1)	25(1)
O(2)	-323(3)	3558(5)	1681(1)	60(1)
C(2)	1277(4)	-1846(10)	3314(1)	55(1)
O(3)	1506(2)	-4450(4)	541(1)	31(1)
C(3)	2185(4)	-733(10)	3487(1)	56(1)
C(4)	2626(4)	1366(11)	3307(1)	63(2)
C(5)	2139(4)	2428(10)	2955(1)	59(1)
C(6)	1210(3)	1409(8)	2780(1)	38(1)
C(7)	659(4)	2631(8)	2410(1)	57(1)
C(8)	-138(3)	1239(7)	1770(1)	27(1)
C(9)	-988(3)	-716(7)	1143(1)	24(1)
C(10)	-386(3)	-2162(7)	840(1)	23(1)
C(11)	-582(3)	-1570(8)	406(1)	33(1)
C(12)	426(3)	-637(7)	639(1)	26(1)
C(13)	1421(3)	-1956(6)	564(1)	23(1)
C(14)	3272(3)	-1230(7)	447(1)	28(1)
C(15)	3284(3)	-2179(9)	15(1)	46(1)
C(16)	4059(3)	976(8)	548(1)	46(1)
C(17)	-2114(3)	-1639(7)	1160(1)	28(1)
C(18)	-2576(4)	-3618(9)	922(2)	58(1)
C(19)	-3609(4)	-4372(11)	942(2)	73(2)
C(20)	-4197(4)	-3202(11)	1209(1)	58(1)
C(21)	-3738(4)	-1307(14)	1459(2)	98(2)
C(22)	-2713(4)	-517(12)	1430(2)	79(2)

Table B3. Bond lengths [Å] and angles [°] for corey6s.

O(1)-C(8)	1.351(4)	C(20)-H(20A)	0.95	C(10)-C(11)-H(11A)	117.7
O(1)-C(7)	1.449(4)	C(21)-C(22)	1.384(7)	C(12)-C(11)-H(11A)	117.7
N(1)-C(8)	1.330(4)	C(21)-H(21A)	0.95	C(10)-C(11)-H(11B)	117.7
N(1)-C(9)	1.463(4)	C(22)-H(22A)	0.95	C(12)-C(11)-H(11B)	117.7
N(1)-H(1N)	0.93(4)	C(8)-O(1)-C(7)	115.8(3)	H(11A)-C(11)-H(11B)	114.9
C(1)-C(2)	1.378(6)	C(8)-N(1)-C(9)	123.3(3)	C(13)-C(12)-C(10)	120.2(3)
C(1)-C(6)	1.385(6)	C(8)-N(1)-H(1N)	115(3)	C(13)-C(12)-C(11)	119.0(3)
C(1)-H(1A)	0.95	C(9)-N(1)-H(1N)	121(3)	C(10)-C(12)-C(11)	58.6(2)
N(2)-C(13)	1.349(4)	C(2)-C(1)-C(6)	120.7(4)	C(13)-C(12)-H(12A)	115.7
N(2)-C(14)	1.463(4)	C(2)-C(1)-H(1A)	119.6	C(10)-C(12)-H(12A)	115.7
N(2)-H(2N)	0.82(4)	C(6)-C(1)-H(1A)	119.6	C(11)-C(12)-H(12A)	115.7
O(2)-C(8)	1.206(4)	C(13)-N(2)-C(14)	122.8(3)	O(3)-C(13)-N(2)	122.4(3)
C(2)-C(3)	1.363(6)	C(13)-N(2)-H(2N)	120(3)	O(3)-C(13)-C(12)	122.2(3)
C(2)-H(2A)	0.95	C(14)-N(2)-H(2N)	118(3)	N(2)-C(13)-C(12)	115.4(3)
O(3)-C(13)	1.246(4)	C(3)-C(2)-C(1)	120.1(4)	N(2)-C(14)-C(16)	109.3(3)
C(3)-C(4)	1.355(6)	C(3)-C(2)-H(2A)	120	N(2)-C(14)-C(15)	111.2(3)
C(3)-H(3A)	0.95	C(1)-C(2)-H(2A)	120	C(16)-C(14)-C(15)	111.5(3)
C(4)-C(5)	1.378(6)	C(4)-C(3)-C(2)	120.1(4)	N(2)-C(14)-H(14A)	108.3
C(4)-H(4A)	0.95	C(4)-C(3)-H(3A)	120	C(16)-C(14)-H(14A)	108.3
C(5)-C(6)	1.370(6)	C(2)-C(3)-H(3A)	120	C(15)-C(14)-H(14A)	108.3
C(5)-H(5A)	0.95	C(3)-C(4)-C(5)	120.0(4)	C(14)-C(15)-H(15A)	109.5
C(6)-C(7)	1.487(6)	C(3)-C(4)-H(4A)	120	C(14)-C(15)-H(15B)	109.5
C(7)-H(7A)	0.99	C(5)-C(4)-H(4A)	120	H(15A)-C(15)-H(15B)	109.5
C(7)-H(7B)	0.99	C(6)-C(5)-C(4)	121.4(4)	C(14)-C(15)-H(15C)	109.5
C(9)-C(10)	1.513(5)	C(6)-C(5)-H(5A)	119.3	H(15A)-C(15)-H(15C)	109.5
C(9)-C(17)	1.522(5)	C(4)-C(5)-H(5A)	119.3	H(15B)-C(15)-H(15C)	109.5
C(9)-H(9A)	1	C(5)-C(6)-C(1)	117.7(4)	C(14)-C(16)-H(16A)	109.5
C(10)-C(11)	1.473(5)	C(5)-C(6)-C(7)	121.4(4)	C(14)-C(16)-H(16B)	109.5
C(10)-C(12)	1.499(5)	C(1)-C(6)-C(7)	120.8(4)	H(16A)-C(16)-H(16B)	109.5
C(10)-H(10A)	1	O(1)-C(7)-C(6)	107.9(3)	C(14)-C(16)-H(16C)	109.5
C(11)-C(12)	1.511(5)	O(1)-C(7)-H(7A)	110.1	H(16A)-C(16)-H(16C)	109.5
C(11)-H(11A)	0.99	C(6)-C(7)-H(7A)	110.1	H(16B)-C(16)-H(16C)	109.5
C(11)-H(11B)	0.99	O(1)-C(7)-H(7B)	110.1	C(22)-C(17)-C(18)	116.1(4)
C(12)-C(13)	1.478(5)	C(6)-C(7)-H(7B)	110.1	C(22)-C(17)-C(9)	120.3(4)
C(12)-H(12A)	1	H(7A)-C(7)-H(7B)	108.4	C(18)-C(17)-C(9)	123.5(3)
C(14)-C(16)	1.505(5)	O(2)-C(8)-N(1)	126.0(3)	C(17)-C(18)-C(19)	121.8(4)
C(14)-C(15)	1.519(5)	O(2)-C(8)-O(1)	123.3(3)	C(17)-C(18)-H(18A)	119.1
C(14)-H(14A)	1	N(1)-C(8)-O(1)	110.7(3)	C(19)-C(18)-H(18A)	119.1
C(15)-H(15A)	0.98	N(1)-C(9)-C(10)	109.2(3)	C(20)-C(19)-C(18)	121.0(5)
C(15)-H(15B)	0.98	N(1)-C(9)-C(17)	110.2(3)	C(20)-C(19)-H(19A)	119.5
C(15)-H(15C)	0.98	C(10)-C(9)-C(17)	115.7(3)	C(18)-C(19)-H(19A)	119.5
C(16)-H(16A)	0.98	N(1)-C(9)-H(9A)	107.1	C(21)-C(20)-C(19)	117.9(4)
C(16)-H(16B)	0.98	C(10)-C(9)-H(9A)	107.1	C(21)-C(20)-H(20A)	121.1
C(16)-H(16C)	0.98	C(17)-C(9)-H(9A)	107.1	C(19)-C(20)-H(20A)	121.1
C(17)-C(22)	1.361(6)	C(11)-C(10)-C(12)	61.1(2)	C(20)-C(21)-C(22)	120.7(5)
C(17)-C(18)	1.362(5)	C(11)-C(10)-C(9)	120.9(3)	C(20)-C(21)-H(21A)	119.6
C(18)-C(19)	1.385(6)	C(12)-C(10)-C(9)	118.9(3)	C(22)-C(21)-H(21A)	119.7
C(18)-H(18A)	0.95	C(11)-C(10)-H(10A)	115.1	C(17)-C(22)-C(21)	122.3(5)
C(19)-C(20)	1.355(7)	C(12)-C(10)-H(10A)	115.1	C(17)-C(22)-H(22A)	118.8
C(19)-H(19A)	0.95	C(9)-C(10)-H(10A)	115.1	C(21)-C(22)-H(22A)	118.8
C(20)-C(21)	1.352(7)	C(10)-C(11)-C(12)	60.3(2)		

Table B4. Anisotropic displacement parameters ($Å^2$ x 10^3) for corey6s. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	51(2)	22(1)	30(2)	-5(1)	-10(1)	1(1)
N(1)	27(2)	15(2)	24(2)	0(1)	-1(1)	-1(1)
C(1)	37(3)	64(3)	37(3)	-15(2)	0(2)	-8(2)
N(2)	25(2)	18(2)	32(2)	-2(1)	6(1)	3(1)
O(2)	93(3)	15(1)	61(2)	-1(1)	-37(2)	3(1)
C(2)	58(3)	77(3)	30(2)	-1(2)	3(2)	-20(3)
O(3)	31(2)	19(1)	44(2)	0(1)	10(1)	-2(1)
C(3)	52(3)	82(4)	33(3)	-2(3)	4(2)	3(3)
C(4)	43(3)	107(4)	36(3)	1(3)	-11(2)	-20(3)
C(5)	59(3)	72(3)	44(3)	3(3)	-10(2)	-28(3)
C(6)	41(3)	37(2)	34(2)	-12(2)	-3(2)	2(2)
C(7)	84(4)	31(2)	48(3)	-17(2)	-27(3)	0(2)
C(8)	30(2)	18(2)	31(2)	-2(2)	-2(2)	-1(2)
C(9)	27(2)	24(2)	22(2)	7(2)	2(2)	0(2)
C(10)	22(2)	22(2)	24(2)	1(2)	2(2)	-4(1)
C(11)	24(2)	46(2)	29(2)	3(2)	1(2)	4(2)
C(12)	30(2)	21(2)	27(2)	4(2)	5(2)	1(2)
C(13)	33(2)	16(2)	19(2)	-1(2)	4(2)	-1(2)
C(14)	21(2)	29(2)	35(2)	-1(2)	4(2)	2(2)
C(15)	41(3)	55(3)	45(3)	-3(2)	17(2)	5(2)
C(16)	32(2)	40(2)	66(3)	-2(2)	10(2)	-2(2)
C(17)	28(2)	31(2)	24(2)	6(2)	4(2)	1(2)
C(18)	43(3)	70(3)	64(3)	-29(3)	17(2)	-26(2)
C(19)	47(3)	97(4)	74(4)	-30(3)	11(3)	-38(3)
C(20)	31(3)	94(4)	51(3)	1(3)	7(2)	-23(3)
C(21)	43(3)	160(6)	96(5)	-66(5)	29(3)	-12(4)
C(22)	32(3)	116(5)	93(4)	-63(4)	19(3)	-19(3)

Table B5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for corey6s.

	x	y	z	U(eq)
H(1N)	-260(30)	-2550(90)	1664(12)	50(12)
H(1A)	139	-1523	2849	56
H(2N)	2140(30)	1350(70)	536(11)	27(11)
H(2A)	985	-3366	3435	66
H(3A)	2509	-1430	3735	67
H(4A)	3270	2104	3424	75
H(5A)	2455	3899	2831	71
H(7A)	22	3589	2476	68
H(7B)	1124	3940	2292	68
H(9A)	-1014	1231	1066	29
H(10A)	-204	-4078	908	27
H(11A)	-1115	-189	321	40
H(11B)	-541	-3084	215	40
H(12A)	472	1334	700	31
H(14A)	3460	-2790	630	34
H(15A)	2777	-3644	-39	70
H(15B)	3987	-2826	-26	70
H(15C)	3095	-678	-169	70
H(16A)	4039	1525	829	69
H(16B)	3889	2523	371	69
H(16C)	4763	318	509	69
H(18A)	-2178	-4506	736	70
H(19A)	-3910	-5730	766	87
H(20A)	-4909	-3698	1220	70
H(21A)	-4123	-508	1657	117
H(22A)	-2418	856	1605	95

Appendix C

X-ray crystal data for 372

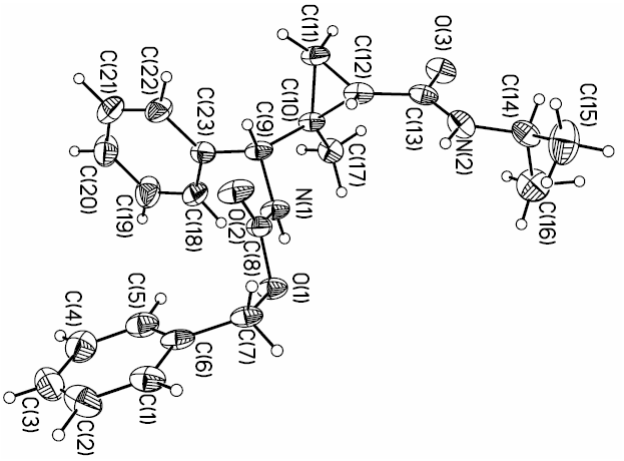


Table C1. Crystal data and structure refinement for cory602s.

Identification code	cory602s	
Empirical formula	$C_{23}H_{28}N_2O_3$	
Formula weight	380.47	
Temperature	150.0 (2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C 2/c	
Unit cell dimensions	a = 16.161(2) Å	α= 90°.
	b = 9.6561(13) Å	β= 94.793(3)°.
	c = 27.197(4) Å	γ = 90°.
Volume	4229.4(10) $Å^3$	
Z	8	
Density (calculated)	1.195 Mg/m^3	
Absorption coefficient	0.079 mm^{-1}	
F(000)	1632	
Crystal size	0.12 x 0.04 x 0.04 mm^3	
Theta range for data collection	1.50 to 25.00°.	
Index ranges	-19<=h<=19, -11<=k<=11, -32<=l<=32	
Reflections collected	16235	
Independent reflections	3732 [R(int) = 0.0691]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	Sadabs	
Max. and min. transmission	0.9968 and 0.9906	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3732 / 0 / 365	
Goodness-of-fit on F^2	1.295	
Final R indices [I>2sigma(I)]	R1 = 0.0828, wR2 = 0.1786	
R indices (all data)	R1 = 0.1116, wR2 = 0.1880	
Largest diff. peak and hole	0.318 and -0.238 $e.Å^{-3}$	

Table C2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for cory602s. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	4250(1)	5052(2)	1938(1)	31(1)
C(1)	5563(2)	7398(4)	1243(2)	37(1)
N(1)	3733(2)	2921(3)	1874(1)	28(1)
O(2)	5129(1)	3252(2)	1862(1)	37(1)
C(2)	5659(2)	7765(4)	764(2)	50(1)
N(2)	3569(2)	1341(3)	3410(1)	31(1)
O(3)	2847(1)	-572(2)	3167(1)	33(1)
C(3)	5221(2)	7117(5)	372(2)	50(1)
C(4)	4671(2)	6086(4)	472(2)	44(1)
C(5)	4571(2)	5702(4)	951(1)	38(1)
C(6)	5008(2)	6343(3)	1344(1)	32(1)
C(7)	4928(2)	5971(3)	1873(1)	29(1)
C(8)	4428(2)	3689(3)	1887(1)	27(1)
C(9)	3761(2)	1449(3)	1762(1)	27(1)
C(10)	3297(2)	594(3)	2125(1)	24(1)
C(11)	3689(2)	-770(3)	2258(1)	32(1)
C(12)	3786(2)	390(3)	2623(1)	28(1)
C(13)	3354(2)	342(3)	3086(1)	28(1)
C(14)	3202(2)	1530(4)	3878(1)	36(1)
C(15)	3806(3)	2251(6)	4241(2)	61(1)
C(16)	2376(3)	2281(5)	3800(2)	52(1)
C(17)	2357(2)	743(4)	2097(2)	30(1)
C(18)	2785(2)	1671(4)	977(1)	41(1)
C(19)	2560(3)	1319(5)	497(2)	51(1)
C(20)	3040(3)	423(4)	245(2)	48(1)
C(21)	3755(2)	-93(4)	481(2)	47(1)
C(22)	3983(2)	253(4)	964(2)	39(1)
C(23)	3505(2)	1133(3)	1226(1)	29(1)

Table C3. Bond lengths [Å] and angles [°] for cory602s.

O(1)-C(8)	1.357(4)	C(21)-C(22)	1.376(5)	C(12)-C(11)-H(11C)	120(2)
O(1)-C(7)	1.432(4)	C(21)-H(21)	1.01(4)	H(11B)-C(11)-H(11C)	110(3)
C(1)-C(2)	1.370(6)	C(22)-C(23)	1.386(5)	C(13)-C(12)-C(11)	120.4(3)
C(1)-C(6)	1.399(5)	C(22)-H(22)	0.98(4)	C(13)-C(12)-C(10)	120.7(2)
C(1)-H(1)	1.06(4)	C(8)-O(1)-C(7)	114.7(2)	C(11)-C(12)-C(10)	59.3(2)
N(1)-C(8)	1.344(4)	C(2)-C(1)-C(6)	120.0(4)	C(13)-C(12)-H(12)	112.9(19)
N(1)-C(9)	1.456(4)	C(2)-C(1)-H(1)	123(2)	C(11)-C(12)-H(12)	122(2)
N(1)-H(1N)	0.82(4)	C(6)-C(1)-H(1)	117(2)	C(10)-C(12)-H(12)	111(2)
O(2)-C(8)	1.215(3)	C(8)-N(1)-C(9)	120.2(3)	O(3)-C(13)-N(2)	122.5(3)
C(2)-C(3)	1.379(6)	C(8)-N(1)-H(1N)	114(3)	O(3)-C(13)-C(12)	122.5(3)
C(2)-H(2)	0.98(4)	C(9)-N(1)-H(1N)	124(3)	N(2)-C(13)-C(12)	115.0(3)
N(2)-C(13)	1.334(4)	C(1)-C(2)-C(3)	121.7(4)	N(2)-C(14)-C(15)	110.0(3)
N(2)-C(14)	1.459(5)	C(1)-C(2)-H(2)	125(2)	N(2)-C(14)-C(16)	110.8(3)
N(2)-H(2N)	0.78(4)	C(3)-C(2)-H(2)	113(2)	C(15)-C(14)-C(16)	112.7(4)
O(3)-C(13)	1.237(4)	C(13)-N(2)-C(14)	124.4(3)	N(2)-C(14)-H(14)	106(2)
C(3)-C(4)	1.377(6)	C(13)-N(2)-H(2N)	115(3)	C(15)-C(14)-H(14)	107(2)
C(3)-H(3)	0.88(4)	C(14)-N(2)-H(2N)	119(3)	C(16)-C(14)-H(14)	109(2)
C(4)-C(5)	1.375(6)	C(4)-C(3)-C(2)	118.2(4)	C(14)-C(15)-H(15B)	115(3)
C(4)-H(4)	0.90(4)	C(4)-C(3)-H(3)	119(2)	C(14)-C(15)-H(15C)	105(2)
C(5)-C(6)	1.378(5)	C(2)-C(3)-H(3)	122(2)	H(15B)-C(15)-H(15C)	104(3)
C(5)-H(5)	0.93(4)	C(5)-C(4)-C(3)	120.7(4)	C(14)-C(15)-H(15A)	110(3)
C(6)-C(7)	1.498(5)	C(5)-C(4)-H(4)	120(2)	H(15B)-C(15)-H(15A)	114(4)
C(7)-H(7A)	0.95(3)	C(3)-C(4)-H(4)	119(2)	H(15C)-C(15)-H(15A)	108(4)
C(7)-H(7B)	1.01(4)	C(4)-C(5)-C(6)	121.4(4)	C(14)-C(16)-H(16A)	102(2)
C(9)-C(23)	1.511(5)	C(4)-C(5)-H(5)	121(2)	C(14)-C(16)-H(16B)	105(2)
C(9)-C(10)	1.531(4)	C(6)-C(5)-H(5)	117(2)	H(16A)-C(16)-H(16B)	116(3)
C(9)-H(9)	1.00(3)	C(5)-C(6)-C(1)	118.0(3)	C(14)-C(16)-H(16C)	109(3)
C(10)-C(11)	1.493(4)	C(5)-C(6)-C(7)	123.9(3)	H(16A)-C(16)-H(16C)	110(4)
C(10)-C(17)	1.521(4)	C(1)-C(6)-C(7)	118.1(3)	H(16B)-C(16)-H(16C)	114(4)
C(10)-C(12)	1.522(4)	O(1)-C(7)-C(6)	113.4(3)	C(10)-C(17)-H(17A)	115.0(19)
C(11)-C(12)	1.496(5)	O(1)-C(7)-H(7A)	101.2(19)	C(10)-C(17)-H(17B)	108.2(19)
C(11)-H(11B)	0.98(3)	C(6)-C(7)-H(7A)	114.4(18)	H(17A)-C(17)-H(17B)	109(3)
C(11)-H(11C)	0.97(4)	O(1)-C(7)-H(7B)	111(2)	C(10)-C(17)-H(17C)	112(2)
C(12)-C(13)	1.490(5)	C(6)-C(7)-H(7B)	112(2)	H(17A)-C(17)-H(17C)	105(3)
C(12)-H(12)	1.02(4)	H(7A)-C(7)-H(7B)	104(3)	H(17B)-C(17)-H(17C)	108(3)
C(14)-C(15)	1.500(5)	O(2)-C(8)-N(1)	126.0(3)	C(19)-C(18)-C(23)	121.0(4)
C(14)-C(16)	1.519(5)	O(2)-C(8)-O(1)	123.3(3)	C(19)-C(18)-H(18)	125(2)
C(14)-H(14)	0.90(4)	N(1)-C(8)-O(1)	110.7(3)	C(23)-C(18)-H(18)	114(2)
C(15)-H(15B)	0.97(5)	N(1)-C(9)-C(23)	112.9(3)	C(18)-C(19)-C(20)	120.9(4)
C(15)-H(15C)	1.00(4)	N(1)-C(9)-C(10)	111.4(3)	C(18)-C(19)-H(19)	122(3)
C(15)-H(15A)	1.07(6)	C(23)-C(9)-C(10)	113.8(3)	C(20)-C(19)-H(19)	117(3)
C(16)-H(16A)	1.07(5)	N(1)-C(9)-H(9)	105.6(18)	C(21)-C(20)-C(19)	118.9(4)
C(16)-H(16B)	1.04(5)	C(23)-C(9)-H(9)	104.1(17)	C(21)-C(20)-H(20)	122(2)
C(16)-H(16C)	1.05(5)	C(10)-C(9)-H(9)	108.4(18)	C(19)-C(20)-H(20)	120(2)
C(17)-H(17A)	0.99(4)	C(11)-C(10)-C(17)	119.8(3)	C(20)-C(21)-C(22)	120.5(4)
C(17)-H(17B)	0.91(3)	C(11)-C(10)-C(12)	59.5(2)	C(20)-C(21)-H(21)	119(2)
C(17)-H(17C)	0.93(4)	C(17)-C(10)-C(12)	119.9(3)	C(22)-C(21)-H(21)	120(2)
C(18)-C(19)	1.368(5)	C(11)-C(10)-C(9)	114.3(3)	C(21)-C(22)-C(23)	121.6(4)
C(18)-C(23)	1.397(5)	C(17)-C(10)-C(9)	117.2(3)	C(21)-C(22)-H(22)	122(2)
C(18)-H(18)	0.90(3)	C(12)-C(10)-C(9)	113.5(2)	C(23)-C(22)-H(22)	116(2)
C(19)-C(20)	1.382(6)	C(10)-C(11)-C(12)	61.2(2)	C(22)-C(23)-C(18)	117.1(3)
C(19)-H(19)	0.95(4)	C(10)-C(11)-H(11B)	123.7(19)	C(22)-C(23)-C(9)	120.0(3)
C(20)-C(21)	1.368(6)	C(12)-C(11)-H(11B)	116.8(19)	C(18)-C(23)-C(9)	122.9(3)
C(20)-H(20)	0.94(4)	C(10)-C(11)-H(11C)	118(2)		

Table C4. Anisotropic displacement parameters ($Å^2$ x 10^3) for cory602s. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	22(1)	22(1)	51(2)	2(1)	9(1)	2(1)
C(1)	20(2)	31(2)	59(3)	6(2)	2(2)	3(1)
N(1)	14(1)	22(2)	48(2)	2(1)	5(1)	4(1)
O(2)	13(1)	29(1)	70(2)	-1(1)	8(1)	3(1)
C(2)	27(2)	50(3)	75(3)	24(2)	13(2)	3(2)
N(2)	24(2)	32(2)	37(2)	7(1)	2(1)	-14(1)
O(3)	21(1)	30(1)	48(2)	8(1)	1(1)	-12(1)
C(3)	39(2)	62(3)	50(3)	22(2)	14(2)	18(2)
C(4)	36(2)	52(3)	44(2)	-2(2)	-1(2)	8(2)
C(5)	28(2)	31(2)	56(3)	0(2)	3(2)	5(2)
C(6)	21(2)	20(2)	53(2)	-1(2)	-1(2)	5(1)
C(7)	23(2)	17(2)	48(2)	-3(2)	0(2)	-2(1)
C(8)	25(2)	21(2)	35(2)	4(1)	6(1)	3(1)
C(9)	14(2)	21(2)	46(2)	2(1)	6(1)	3(1)
C(10)	13(2)	20(2)	38(2)	2(1)	1(1)	0(1)
C(11)	26(2)	23(2)	48(2)	4(2)	7(2)	6(2)
C(12)	14(2)	23(2)	46(2)	3(1)	-1(1)	-3(1)
C(13)	17(2)	24(2)	41(2)	8(1)	-4(1)	0(1)
C(14)	34(2)	33(2)	39(2)	10(2)	0(2)	-7(2)
C(15)	48(3)	91(4)	44(3)	-16(3)	-1(2)	-8(3)
C(16)	34(2)	61(3)	61(3)	4(2)	6(2)	2(2)
C(17)	14(2)	36(2)	38(2)	3(2)	2(2)	-2(1)
C(18)	40(2)	42(2)	41(2)	0(2)	10(2)	17(2)
C(19)	42(2)	73(3)	37(2)	2(2)	5(2)	18(2)
C(20)	49(2)	61(3)	35(2)	-2(2)	8(2)	3(2)
C(21)	47(2)	47(2)	48(2)	-7(2)	14(2)	14(2)
C(22)	33(2)	38(2)	47(2)	0(2)	11(2)	10(2)
C(23)	20(2)	27(2)	41(2)	5(1)	9(1)	1(1)

Table C5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for cory602s.

	x	y	z	U(eq)
H(1)	5910(20)	7850(40)	1548(15)	59(12)
H(1N)	3310(20)	3370(40)	1856(12)	37(10)
H(2)	5980(20)	8560(40)	665(14)	52(11)
H(2N)	3840(20)	1930(40)	3313(12)	31(10)
H(3)	5280(20)	7340(40)	64(14)	40(11)
H(4)	4390(20)	5640(40)	219(14)	37(10)
H(5)	4230(20)	4970(40)	1019(14)	55(12)
H(7A)	4796(18)	6720(30)	2074(11)	24(8)
H(7B)	5460(20)	5610(40)	2039(12)	41(10)
H(9)	4360(20)	1190(30)	1803(11)	27(8)
H(11B)	3380(20)	-1580(40)	2354(11)	32(9)
H(11C)	4160(20)	-1070(40)	2081(13)	48(11)
H(12)	4300(20)	1000(40)	2652(12)	44(10)
H(14)	3120(20)	680(40)	3996(13)	38(10)
H(15B)	3600(30)	2460(40)	4556(17)	65(13)
H(15C)	3890(20)	3180(50)	4090(15)	57(13)
H(15A)	4380(40)	1710(60)	4270(20)	108(19)
H(16A)	2140(30)	2180(50)	4155(18)	75(14)
H(16B)	2520(30)	3280(50)	3695(16)	73(14)
H(16C)	1990(30)	1740(50)	3538(18)	87(16)
H(17A)	2150(20)	1700(40)	2136(11)	33(9)
H(17B)	2162(18)	200(30)	2335(11)	20(8)
H(17C)	2110(20)	450(40)	1792(14)	41(10)
H(18)	2540(20)	2330(30)	1145(11)	26(9)
H(19)	2080(30)	1690(50)	320(16)	70(14)
H(20)	2880(20)	210(40)	-88(15)	47(11)
H(21)	4110(20)	-740(40)	298(13)	43(10)
H(22)	4450(30)	-190(40)	1151(14)	58(12)

Appendix D

X-ray crystal data for 380

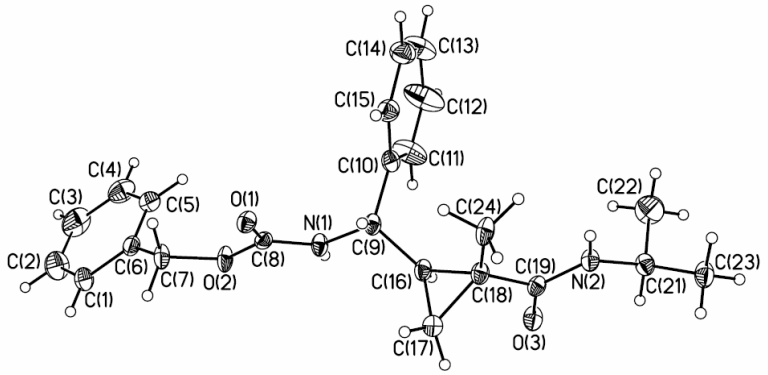


Table D1. Crystal data and structure refinement for cs206m.

Identification code	cs206m	
Empirical formula	C23 H28 N2 O3 – $(C7 H8)_{0.5}$	
Formula weight	426.54	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 11.6314(12) Å	α= 90°.
	b = 13.4650(14) Å	β= 101.713(2)°.
	c = 16.1777(17) Å	γ = 90°.
Volume	2480.9(4) $Å^3$	
Z	4	
Density (calculated)	1.142 Mg/m^3	
Absorption coefficient	0.074 mm^{-1}	
F(000)	916	
Crystal size	0.35 x 0.21 x 0.21 mm^3	
Theta range for data collection	1.98 to 32.58°.	
Index ranges	-17<=h<=17, -19<=k<=20, -23<=l<=23	
Reflections collected	31166	
Independent reflections	8692 [R(int) = 0.0814]	
Completeness to theta = 32.58°	96.2 %	
Absorption correction	Sadabs	
Max. and min. transmission	0.9845 and 0.9744	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8692 / 0 / 297	
Goodness-of-fit on F^2	0.929	
Final R indices [I>2sigma(I)]	R1 = 0.0618, wR2 = 0.1537	
R indices (all data)	R1 = 0.1142, wR2 = 0.1715	
Largest diff. peak and hole	0.439 and -0.399 $e.Å^{-3}$	

Table D2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for cs206m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	8724(1)	2652(1)	1498(1)	29(1)
O(2)	7662(1)	1977(1)	304(1)	34(1)
C(1)	8387(2)	-245(1)	-638(1)	43(1)
N(1)	7000(1)	3327(1)	821(1)	27(1)
C(2)	7856(2)	-1133(2)	-956(1)	64(1)
O(3)	5181(1)	6746(1)	365(1)	35(1)
C(3)	6879(2)	-1471(2)	-693(2)	67(1)
C(4)	6408(2)	-939(2)	-123(1)	55(1)
C(5)	6925(2)	-63(1)	196(1)	40(1)
C(6)	7926(1)	289(1)	-50(1)	31(1)
C(7)	8531(1)	1206(1)	343(1)	34(1)
C(8)	7864(1)	2664(1)	931(1)	24(1)
C(9)	6956(1)	4122(1)	1429(1)	26(1)
C(10)	6176(1)	3840(1)	2041(1)	30(1)
C(11)	4981(2)	3707(2)	1759(1)	58(1)
C(12)	4279(2)	3429(2)	2314(1)	78(1)
C(13)	4771(2)	3266(2)	3156(1)	59(1)
C(14)	5942(2)	3422(1)	3447(1)	45(1)
C(15)	6638(1)	3714(1)	2889(1)	35(1)
C(16)	6549(1)	5062(1)	951(1)	28(1)
C(17)	7396(2)	5765(1)	684(1)	37(1)
C(18)	6763(1)	6071(1)	1376(1)	27(1)
C(19)	5755(1)	6775(1)	1097(1)	26(1)
N(2)	5514(1)	7421(1)	1665(1)	28(1)
C(20)	4495(1)	8081(1)	1498(1)	30(1)
C(21)	3497(2)	7640(2)	1839(2)	61(1)
C(22)	4824(2)	9102(1)	1865(1)	40(1)
C(23)	7461(1)	6142(1)	2268(1)	34(1)
C(24)	9731(4)	5801(2)	-524(3)	109(1)
C(25)	10534(4)	5898(2)	197(3)	111(1)
C(26)	10831(4)	5100(3)	731(3)	107(1)
C(27)	11602(6)	5192(5)	1387(4)	98(2)

Table D3. Bond lengths [Å] and angles [°] for cs206m.

O(1)-C(8)	1.2114(16)	C(25)-H(25A)	0.95	C(17)-C(16)-C(18)	60.43(10)
O(2)-C(8)	1.3576(16)	C(26)-C(27)	1.248(6)	C(9)-C(16)-C(18)	120.77(12)
O(2)-C(7)	1.4415(17)	C(26)-C(24)#1	1.386(5)	C(17)-C(16)-H(16A)	114.5
C(1)-C(6)	1.384(2)	C(27)-H(27A)	0.98	C(9)-C(16)-H(16A)	114.5
C(1)-C(2)	1.394(3)	C(27)-H(27B)	0.98	C(18)-C(16)-H(16A)	114.5
C(1)-H(1A)	0.95	C(27)-H(27C)	0.98	C(16)-C(17)-C(18)	60.77(10)
N(1)-C(8)	1.3295(18)	C(8)-O(2)-C(7)	116.36(11)	C(16)-C(17)-H(17A)	117.7
N(1)-C(9)	1.4623(17)	C(6)-C(1)-C(2)	119.56(18)	C(18)-C(17)-H(17A)	117.7
N(1)-H(1N)	0.826(18)	C(6)-C(1)-H(1A)	120.2	C(16)-C(17)-H(17B)	117.7
C(2)-C(3)	1.369(3)	C(2)-C(1)-H(1A)	120.2	C(18)-C(17)-H(17B)	117.7
C(2)-H(2A)	0.95	C(8)-N(1)-C(9)	121.99(12)	H(17A)-C(17)-H(17B)	114.8
O(3)-C(19)	1.2373(16)	C(8)-N(1)-H(1N)	118.8(12)	C(19)-C(18)-C(23)	118.91(12)
C(3)-C(4)	1.367(3)	C(9)-N(1)-H(1N)	118.8(12)	C(19)-C(18)-C(17)	114.55(12)
C(3)-H(3A)	0.95	C(3)-C(2)-C(1)	120.28(18)	C(23)-C(18)-C(17)	118.36(13)
C(4)-C(5)	1.376(3)	C(3)-C(2)-H(2A)	119.9	C(19)-C(18)-C(16)	112.42(11)
C(4)-H(4A)	0.95	C(1)-C(2)-H(2A)	119.9	C(23)-C(18)-C(16)	119.75(12)
C(5)-C(6)	1.388(2)	C(4)-C(3)-C(2)	120.47(19)	C(17)-C(18)-C(16)	58.80(10)
C(5)-H(5A)	0.95	C(4)-C(3)-H(3A)	119.8	O(3)-C(19)-N(2)	122.14(13)
C(6)-C(7)	1.498(2)	C(2)-C(3)-H(3A)	119.8	O(3)-C(19)-C(18)	120.26(13)
C(7)-H(7A)	0.99	C(3)-C(4)-C(5)	119.80(19)	N(2)-C(19)-C(18)	117.60(12)
C(7)-H(7B)	0.99	C(3)-C(4)-H(4A)	120.1	C(19)-N(2)-C(20)	122.99(12)
C(9)-C(16)	1.509(2)	C(5)-C(4)-H(4A)	120.1	C(19)-N(2)-H(2N)	117.4(12)
C(9)-C(10)	1.521(2)	C(4)-C(5)-C(6)	120.87(17)	C(20)-N(2)-H(2N)	118.7(12)
C(9)-H(9A)	1	C(4)-C(5)-H(5A)	119.6	N(2)-C(20)-C(21)	110.39(14)
C(10)-C(15)	1.378(2)	C(6)-C(5)-H(5A)	119.6	N(2)-C(20)-C(22)	110.41(12)
C(10)-C(11)	1.384(2)	C(1)-C(6)-C(5)	119.01(16)	C(21)-C(20)-C(22)	111.54(15)
C(11)-C(12)	1.384(3)	C(1)-C(6)-C(7)	120.38(15)	N(2)-C(20)-H(20A)	108.1
C(11)-H(11A)	0.95	C(5)-C(6)-C(7)	120.55(14)	C(21)-C(20)-H(20A)	108.1
C(12)-C(13)	1.383(3)	O(2)-C(7)-C(6)	108.08(12)	C(22)-C(20)-H(20A)	108.1
C(12)-H(12A)	0.95	O(2)-C(7)-H(7A)	110.1	C(20)-C(21)-H(21A)	109.5
C(13)-C(14)	1.364(3)	C(6)-C(7)-H(7A)	110.1	C(20)-C(21)-H(21B)	109.5
C(13)-H(13A)	0.95	O(2)-C(7)-H(7B)	110.1	H(21A)-C(21)-H(21B)	109.5
C(14)-C(15)	1.387(2)	C(6)-C(7)-H(7B)	110.1	C(20)-C(21)-H(21C)	109.5
C(14)-H(14A)	0.95	H(7A)-C(7)-H(7B)	108.4	H(21A)-C(21)-H(21C)	109.5
C(15)-H(15A)	0.95	O(1)-C(8)-N(1)	126.60(13)	H(21B)-C(21)-H(21C)	109.5
C(16)-C(17)	1.491(2)	O(1)-C(8)-O(2)	123.21(12)	C(20)-C(22)-H(22A)	109.5
C(16)-C(18)	1.5215(19)	N(1)-C(8)-O(2)	110.19(11)	C(20)-C(22)-H(22B)	109.5
C(16)-H(16A)	1	N(1)-C(9)-C(16)	108.59(11)	H(22A)-C(22)-H(22B)	109.5
C(17)-C(18)	1.516(2)	N(1)-C(9)-C(10)	111.25(11)	C(20)-C(22)-H(22C)	109.5
C(17)-H(17A)	0.99	C(16)-C(9)-C(10)	112.13(12)	H(22A)-C(22)-H(22C)	109.5
C(17)-H(17B)	0.99	N(1)-C(9)-H(9A)	108.3	H(22B)-C(22)-H(22C)	109.5
C(18)-C(19)	1.504(2)	C(16)-C(9)-H(9A)	108.3	C(18)-C(23)-H(23A)	109.5
C(18)-C(23)	1.5079(19)	C(10)-C(9)-H(9A)	108.3	C(18)-C(23)-H(23B)	109.5
C(19)-N(2)	1.3342(18)	C(15)-C(10)-C(11)	118.39(15)	H(23A)-C(23)-H(23B)	109.5
N(2)-C(20)	1.4624(18)	C(15)-C(10)-C(9)	121.00(13)	C(18)-C(23)-H(23C)	109.5
N(2)-H(2N)	0.814(16)	C(11)-C(10)-C(9)	120.61(14)	H(23A)-C(23)-H(23C)	109.5
C(20)-C(21)	1.505(2)	C(10)-C(11)-C(12)	120.43(18)	H(23B)-C(23)-H(23C)	109.5
C(20)-C(22)	1.514(2)	C(10)-C(11)-H(11A)	119.8	C(25)-C(24)-C(26)#1	120.3(4)

Table D3. Cont'd

C(20)-H(20A)	1	C(12)-C(11)-H(11A)	119.8	C(25)-C(24)-H(24A)	119.8
C(21)-H(21A)	0.98	C(13)-C(12)-C(11)	120.1(2)	C(26)#1-C(24)-H(24A)	119.8
C(21)-H(21B)	0.98	C(13)-C(12)-H(12A)	119.9	C(24)-C(25)-C(26)	120.6(4)
C(21)-H(21C)	0.98	C(11)-C(12)-H(12A)	119.9	C(24)-C(25)-H(25A)	119.7
C(22)-H(22A)	0.98	C(14)-C(13)-C(12)	119.97(18)	C(26)-C(25)-H(25A)	119.7
C(22)-H(22B)	0.98	C(14)-C(13)-H(13A)	120	C(27)-C(26)-C(25)	120.0(5)
C(22)-H(22C)	0.98	C(12)-C(13)-H(13A)	120	C(27)-C(26)-C(24)#1	121.0(5)
C(23)-H(23A)	0.98	C(13)-C(14)-C(15)	119.59(17)	C(25)-C(26)-C(24)#1	119.0(4)
C(23)-H(23B)	0.98	C(13)-C(14)-H(14A)	120.2	C(26)-C(27)-H(27A)	109.5
C(23)-H(23C)	0.98	C(15)-C(14)-H(14A)	120.2	C(26)-C(27)-H(27B)	109.5
C(24)-C(25)	1.345(5)	C(10)-C(15)-C(14)	121.43(16)	H(27A)-C(27)-H(27B)	109.5
C(24)-C(26)#1	1.386(5)	C(10)-C(15)-H(15A)	119.3	C(26)-C(27)-H(27C)	109.5
C(24)-H(24A)	0.95	C(14)-C(15)-H(15A)	119.3	H(27A)-C(27)-H(27C)	109.5
C(25)-C(26)	1.378(5)	C(17)-C(16)-C(9)	121.59(13)	H(27B)-C(27)-H(27C)	109.5

Symmetry transformations used to generate equivalent atoms: #1 -x+2,-y+1,-z

Table D4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for cs206m. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	32(1)	25(1)	26(1)	-1(1)	-1(1)	2(1)
O(2)	40(1)	27(1)	31(1)	-11(1)	-5(1)	13(1)
C(1)	58(1)	32(1)	43(1)	-6(1)	19(1)	9(1)
N(1)	29(1)	24(1)	25(1)	-8(1)	-3(1)	5(1)
C(2)	99(2)	38(1)	59(1)	-21(1)	26(1)	4(1)
O(3)	40(1)	32(1)	28(1)	-6(1)	-5(1)	6(1)
C(3)	96(2)	32(1)	69(1)	-11(1)	7(1)	-15(1)
C(4)	65(1)	40(1)	59(1)	8(1)	10(1)	-11(1)
C(5)	48(1)	37(1)	36(1)	4(1)	11(1)	5(1)
C(6)	39(1)	24(1)	28(1)	1(1)	6(1)	7(1)
C(7)	36(1)	27(1)	38(1)	-6(1)	4(1)	12(1)
C(8)	31(1)	19(1)	22(1)	1(1)	6(1)	0(1)
C(9)	30(1)	20(1)	26(1)	-6(1)	2(1)	1(1)
C(10)	34(1)	23(1)	31(1)	-9(1)	6(1)	-2(1)
C(11)	41(1)	98(2)	36(1)	-14(1)	7(1)	-20(1)
C(12)	52(1)	136(2)	48(1)	-22(1)	17(1)	-40(1)
C(13)	63(1)	77(2)	45(1)	-15(1)	26(1)	-28(1)
C(14)	56(1)	45(1)	34(1)	-3(1)	13(1)	-4(1)
C(15)	37(1)	34(1)	33(1)	0(1)	4(1)	0(1)
C(16)	33(1)	23(1)	26(1)	-5(1)	1(1)	4(1)
C(17)	43(1)	32(1)	39(1)	4(1)	15(1)	7(1)
C(18)	29(1)	23(1)	29(1)	-4(1)	2(1)	1(1)
C(19)	28(1)	22(1)	27(1)	-1(1)	1(1)	-1(1)
N(2)	29(1)	27(1)	23(1)	-3(1)	-4(1)	6(1)
C(20)	27(1)	32(1)	29(1)	-1(1)	1(1)	7(1)
C(21)	40(1)	67(1)	79(2)	8(1)	20(1)	0(1)
C(22)	46(1)	32(1)	37(1)	-3(1)	1(1)	13(1)
C(23)	36(1)	22(1)	37(1)	-7(1)	-7(1)	5(1)
C(24)	150(3)	55(2)	159(3)	14(2)	120(3)	-3(2)
C(25)	160(4)	57(2)	156(3)	1(2)	124(3)	-13(2)
C(26)	129(3)	82(2)	144(3)	-2(2)	105(3)	-14(2)
C(27)	96(4)	110(5)	92(5)	7(4)	28(4)	-47(4)

Table D5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for cs206m.

	x	y	z	U(eq)
H(1A)	9061	-9	-824	52
H(1N)	6435(16)	3252(13)	424(11)	36(5)
H(2A)	8173	-1504	-1356	77
H(3A)	6526	-2079	-909	80
H(4A)	5725	-1174	53	66
H(5A)	6593	307	590	48
H(7A)	8912	1074	937	41
H(7B)	9143	1415	34	41
H(9A)	7770	4234	1761	31
H(11A)	4641	3808	1179	70
H(12A)	3457	3349	2117	94
H(13A)	4293	3046	3532	71
H(14A)	6278	3330	4028	54
H(15A)	7451	3831	3095	42
H(16A)	5782	5000	542	34
H(17A)	7158	6090	127	44
H(17B)	8242	5607	850	44
H(2N)	5884(14)	7369(12)	2147(11)	27(4)
H(20A)	4236	8151	872	36
H(21A)	3305	6982	1589	91
H(21B)	2808	8073	1697	91
H(21C)	3728	7576	2454	91
H(22A)	5471	9369	1627	59
H(22B)	5071	9051	2479	59
H(22C)	4144	9544	1724	59
H(23A)	6944	6346	2645	51
H(23B)	8090	6633	2292	51
H(23C)	7805	5493	2446	51
H(24A)	9548	6352	-894	131
H(25A)	10900	6523	340	134
H(27A)	11899	5875	1428	147
H(27B)	12248	4732	1368	147
H(27C)	11263	5041	1880	147

Appendix E

X-ray crystal data for 390

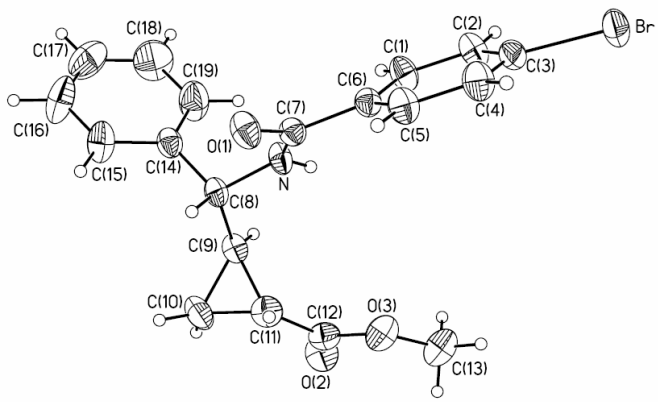


Table E1. Crystal data and structure refinement for corey70s.

Identification code	corey70s	
Empirical formula	$C_{19}H_{18}BrNO_3$	
Formula weight	388.25	
Temperature	571(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 5.3668(3) Å	α= 90°.
	b = 14.3480(7) Å	β= 90°.
	c = 23.0874(11) Å	γ = 90°.
Volume	1777.80(16) $Å^3$	
Z	4	
Density (calculated)	1.451 Mg/m^3	
Absorption coefficient	2.328 mm^{-1}	
F(000)	792	
Crystal size	0.20 x 0.20 x 0.20 mm^3	
Theta range for data collection	1.67 to 32.50°.	
Index ranges	-8<=h<=8, -21<=k<=21, -34<=l<=34	
Reflections collected	23271	
Independent reflections	6280 [R(int) = 0.0503]	
Completeness to theta = 32.50°	99.2 %	
Absorption correction	None	
Max. and min. transmission	0.6532 and 0.6532	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6280 / 0 / 222	
Goodness-of-fit on F^2	0.955	
Final R indices [I>2sigma(I)]	R1 = 0.0432, wR2 = 0.0849	
R indices (all data)	R1 = 0.1031, wR2 = 0.1043	
Absolute structure parameter	0.000(9)	
Largest diff. peak and hole	0.418 and -0.209 e.$Å^{-3}$	

Table E2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for corey70s. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br	540(1)	8523(1)	101(1)	64(1)
O(1)	5378(3)	8602(2)	-2658(1)	53(1)
O(2)	-4945(3)	10722(2)	-3538(1)	66(1)
O(3)	-2742(4)	10928(2)	-2725(1)	63(1)
N	1264(4)	8552(2)	-2842(1)	44(1)
C(1)	569(6)	8000(2)	-1655(1)	51(1)
C(2)	-17(6)	7987(2)	-1072(1)	56(1)
C(3)	1458(5)	8464(2)	-689(1)	48(1)
C(4)	3570(6)	8914(2)	-878(1)	57(1)
C(5)	4148(5)	8926(2)	-1458(1)	51(1)
C(6)	2610(4)	8481(2)	-1854(1)	40(1)
C(7)	3222(4)	8550(2)	-2488(1)	39(1)
C(8)	1448(4)	8680(2)	-3472(1)	39(1)
C(9)	-694(5)	9264(2)	-3664(1)	42(1)
C(10)	-492(7)	9984(2)	-4123(1)	64(1)
C(11)	-671(5)	10286(2)	-3507(1)	51(1)
C(12)	-3018(5)	10672(2)	-3279(1)	50(1)
C(13)	-4998(7)	11206(3)	-2434(2)	79(1)
C(14)	1533(5)	7757(2)	-3787(1)	46(1)
C(15)	3171(6)	7604(3)	-4230(2)	74(1)
C(16)	3168(9)	6768(3)	-4534(2)	97(1)
C(17)	1585(9)	6082(3)	-4394(2)	92(1)
C(18)	-56(10)	6213(3)	-3951(2)	104(2)
C(19)	-78(8)	7054(3)	-3651(2)	81(1)

Table E3. Bond lengths [Å] and angles [°] for corey70s.

Br-C(3)	1.890(2)	C(14)-C(15)	1.367(4)	N-C(8)-C(14)	111.7(2)
O(1)-C(7)	1.224(3)	C(15)-C(16)	1.389(5)	C(9)-C(8)-C(14)	111.9(2)
O(2)-C(12)	1.198(3)	C(16)-C(17)	1.341(6)	C(10)-C(9)-C(8)	123.2(3)
O(3)-C(12)	1.339(4)	C(17)-C(18)	1.363(6)	C(10)-C(9)-C(11)	59.68(19)
O(3)-C(13)	1.441(4)	C(18)-C(19)	1.391(5)	C(8)-C(9)-C(11)	117.9(2)
N-C(7)	1.331(3)	C(12)-O(3)-C(13)	115.4(3)	C(9)-C(10)-C(11)	61.07(17)
N-C(8)	1.470(3)	C(7)-N-C(8)	123.7(2)	C(12)-C(11)-C(10)	120.4(3)
C(1)-C(6)	1.374(4)	C(6)-C(1)-C(2)	120.9(3)	C(12)-C(11)-C(9)	116.3(2)
C(1)-C(2)	1.382(4)	C(3)-C(2)-C(1)	119.4(3)	C(10)-C(11)-C(9)	59.26(18)
C(2)-C(3)	1.371(4)	C(2)-C(3)-C(4)	120.3(2)	O(2)-C(12)-O(3)	123.9(3)
C(3)-C(4)	1.376(4)	C(2)-C(3)-Br	119.7(2)	O(2)-C(12)-C(11)	125.6(3)
C(4)-C(5)	1.374(4)	C(4)-C(3)-Br	120.0(2)	O(3)-C(12)-C(11)	110.5(3)
C(5)-C(6)	1.388(4)	C(5)-C(4)-C(3)	120.0(3)	C(19)-C(14)-C(15)	117.4(3)
C(6)-C(7)	1.503(3)	C(4)-C(5)-C(6)	120.2(3)	C(19)-C(14)-C(8)	121.2(3)
C(8)-C(9)	1.491(4)	C(1)-C(6)-C(5)	119.0(2)	C(15)-C(14)-C(8)	121.3(3)
C(8)-C(14)	1.511(4)	C(1)-C(6)-C(7)	122.2(2)	C(14)-C(15)-C(16)	121.1(4)
C(9)-C(10)	1.483(4)	C(5)-C(6)-C(7)	118.8(2)	C(17)-C(16)-C(15)	120.9(4)
C(9)-C(11)	1.510(4)	O(1)-C(7)-N	123.3(2)	C(16)-C(17)-C(18)	119.2(4)
C(10)-C(11)	1.490(4)	O(1)-C(7)-C(6)	121.5(2)	C(17)-C(18)-C(19)	120.0(4)
C(11)-C(12)	1.474(4)	N-C(7)-C(6)	115.2(2)	C(14)-C(19)-C(18)	121.4(4)
C(14)-C(19)	1.365(4)	N-C(8)-C(9)	108.2(2)		

Table E4. Anisotropic displacement parameters ($Å^2$ x 10^3) for corey70s. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br	80(1)	80(1)	34(1)	-2(1)	5(1)	11(1)
O(1)	35(1)	79(1)	45(1)	7(1)	2(1)	-4(1)
O(2)	37(1)	93(2)	69(1)	2(1)	-9(1)	1(1)
O(3)	52(1)	66(1)	71(1)	-16(1)	-6(1)	1(1)
N	34(1)	65(2)	32(1)	4(1)	5(1)	1(1)
C(1)	53(2)	66(2)	35(1)	0(1)	-3(1)	-15(2)
C(2)	55(2)	72(2)	40(1)	8(1)	4(1)	-7(2)
C(3)	54(2)	55(2)	34(1)	3(1)	-2(1)	13(2)
C(4)	58(2)	70(2)	41(2)	-10(1)	-11(1)	-6(2)
C(5)	45(2)	64(2)	44(1)	-2(1)	-2(1)	-6(1)
C(6)	37(1)	47(1)	35(1)	1(1)	-1(1)	4(1)
C(7)	36(1)	43(1)	38(1)	1(1)	0(1)	0(1)
C(8)	32(1)	53(2)	33(1)	2(1)	3(1)	-4(1)
C(9)	33(1)	55(2)	37(1)	1(1)	-2(1)	-4(1)
C(10)	57(2)	86(2)	49(2)	22(2)	11(2)	6(2)
C(11)	33(1)	56(2)	65(2)	2(1)	0(2)	-7(1)
C(12)	42(2)	45(2)	64(2)	1(1)	-4(1)	-7(1)
C(13)	76(2)	74(2)	88(3)	-20(2)	6(2)	12(2)
C(14)	40(1)	61(2)	37(1)	2(1)	-1(1)	3(1)
C(15)	60(2)	94(3)	67(2)	-14(2)	20(2)	-1(2)
C(16)	87(3)	111(4)	92(3)	-47(3)	26(3)	10(3)
C(17)	99(3)	77(3)	100(3)	-34(2)	-12(3)	17(3)
C(18)	132(4)	68(2)	112(3)	-19(2)	14(3)	-34(3)
C(19)	91(3)	76(2)	77(2)	-16(2)	29(2)	-24(2)

Table E5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for corey70s.

	x	y	z	U(eq)
H(1N)	-140(60)	8630(20)	-2732(12)	45(8)
H(1A)	-433	7679	-1916	61
H(2A)	-1400	7657	-942	67
H(4A)	4607	9212	-613	68
H(5A)	5574	9232	-1585	61
H(8A)	2992	9018	-3556	47
H(9A)	-2327	8962	-3636	50
H(10A)	-1932	10086	-4369	77
H(10B)	1103	10054	-4316	77
H(11A)	867	10522	-3331	62
H(13A)	-4623	11370	-2040	119
H(13B)	-6166	10699	-2438	119
H(13C)	-5708	11734	-2628	119
H(15A)	4306	8066	-4330	88
H(16A)	4279	6684	-4839	116
H(17A)	1605	5522	-4597	110
H(18A)	-1160	5741	-3849	125
H(19A)	-1215	7139	-3351	98

Appendix F

X-ray crystal data for 391

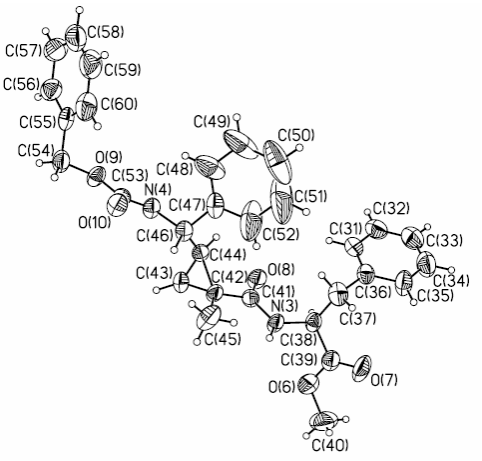


Table F1. Crystal data and structure refinement for cory121s.

Identification code	cory121s	
Empirical formula	$C_{30}H_{32}N_2O_5$	
Formula weight	500.58	
Temperature	295(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 10.4318(5) Å	α= 90°.
	b = 14.7988(6) Å	β= 90°.
	c = 35.7592(15) Å	γ = 90°.
Volume	5520.4(4) $Å^3$	
Z	8	
Density (calculated)	1.205 Mg/m^3	
Absorption coefficient	0.082 mm^{-1}	
F(000)	2128	
Crystal size	0.12 x 0.12 x 0.23 mm^3	
Theta range for data collection	1.49 to 25.00°.	
Index ranges	-12<=h<=12, -17<=k<=17, -42<=l<=42	
Reflections collected	44716	
Independent reflections	9744 [R(int) = 0.1002]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Sadabs	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9744 / 0 / 685	
Goodness-of-fit on F^2	0.950	
Final R indices [I>2sigma(I)]	R1 = 0.0673, wR2 = 0.1393	
R indices (all data)	R1 = 0.1350, wR2 = 0.1639	
Absolute structure parameter	-0.6(15)	
Largest diff. peak and hole	0.177 and -0.140 $e.Å^{-3}$	

Table F2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for cory121s. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)		x	y	z	U(eq)
O(1)	8354(3)	3794(2)	1948(1)	71(1)	C(24)	1871(6)	11232(3)	1537(1)	87(2)
N(1)	6863(3)	5926(2)	2130(1)	41(1)	C(25)	1211(5)	11527(3)	1194(1)	54(1)
C(1)	9178(5)	7111(3)	2419(1)	69(1)	C(26)	1851(6)	11867(4)	901(2)	83(2)
O(2)	6347(3)	4110(2)	2102(1)	70(1)	C(27)	1243(10)	12179(5)	588(2)	117(3)
N(2)	3851(3)	9312(2)	1666(1)	45(1)	C(28)	-39(11)	12155(5)	570(2)	128(4)
C(2)	9575(6)	7996(4)	2369(2)	97(2)	C(29)	-739(7)	11840(4)	856(3)	108(2)
O(3)	6393(3)	6460(2)	1561(1)	66(1)	C(30)	-115(6)	11502(3)	1177(2)	78(2)
C(3)	10357(6)	8210(4)	2082(2)	94(2)	C(31)	5531(6)	11205(4)	1113(2)	85(2)
N(3)	4652(4)	9254(3)	304(1)	66(1)	C(32)	5429(6)	11811(5)	1398(2)	101(2)
O(4)	2577(3)	10405(2)	1460(1)	56(1)	C(33)	5272(7)	12708(5)	1317(2)	109(2)
C(4)	10800(5)	7553(4)	1847(2)	81(2)	C(34)	5230(7)	12972(4)	951(2)	114(2)
N(4)	8065(4)	6324(3)	910(1)	63(1)	C(35)	5314(7)	12361(4)	667(2)	97(2)
O(5)	3085(3)	10352(2)	2070(1)	62(1)	C(36)	5472(5)	11448(3)	746(2)	68(1)
C(5)	10377(4)	6668(3)	1895(1)	64(1)	C(37)	5580(5)	10742(3)	446(2)	83(2)
C(6)	9583(4)	6435(3)	2182(1)	47(1)	C(38)	4342(5)	10178(3)	396(1)	61(1)
O(6)	2425(4)	10071(3)	59(1)	94(1)	C(39)	3433(6)	10593(4)	120(1)	73(2)
C(7)	9095(4)	5480(3)	2226(1)	51(1)	C(40)	1506(8)	10445(5)	-203(2)	153(3)
O(7)	3599(5)	11318(3)	-24(1)	114(2)	C(41)	4914(5)	8655(3)	568(1)	65(1)
C(8)	7852(4)	5317(3)	2006(1)	41(1)	C(42)	5587(6)	7799(3)	455(1)	75(2)
O(8)	4672(4)	8814(2)	898(1)	78(1)	C(43)	5290(6)	6969(3)	685(2)	93(2)
C(9)	7409(4)	4350(3)	2028(1)	46(1)	C(44)	6488(5)	7459(3)	754(1)	61(1)
O(9)	8959(3)	5040(2)	1080(1)	67(1)	C(45)	5930(9)	7683(4)	43(1)	148(4)
C(10)	8049(5)	2832(3)	1956(2)	90(2)	C(46)	7810(5)	7104(3)	670(1)	64(1)
O(10)	9479(3)	5651(2)	519(1)	75(1)	C(47)	8822(6)	7840(3)	714(2)	75(2)
C(11)	6234(4)	6489(3)	1905(1)	38(1)	C(48)	9977(9)	7720(6)	880(2)	134(3)
C(12)	5351(4)	7167(3)	2078(1)	41(1)	C(49)	10892(10)	8430(8)	905(2)	169(5)
C(13)	4008(4)	7166(3)	1919(1)	57(1)	C(50)	10575(14)	9255(8)	755(3)	181(6)
C(14)	4890(4)	7897(2)	1815(1)	41(1)	C(51)	9500(13)	9356(8)	591(5)	254(9)
C(15)	5520(5)	7367(3)	2489(1)	62(1)	C(52)	8589(8)	8669(6)	575(3)	194(5)
C(16)	4704(4)	8859(2)	1938(1)	41(1)	C(53)	8880(5)	5677(3)	809(1)	56(1)
C(17)	5950(4)	9368(2)	1986(1)	42(1)	C(54)	9832(5)	4293(3)	1014(1)	75(2)
C(18)	6181(5)	9872(3)	2299(1)	58(1)	C(55)	11102(5)	4450(3)	1198(2)	69(1)
C(19)	7305(5)	10344(3)	2342(1)	70(1)	C(56)	11378(6)	4048(4)	1532(2)	85(2)
C(20)	8225(5)	10319(3)	2067(2)	74(1)	C(57)	12531(8)	4190(5)	1714(2)	104(2)
C(21)	8014(5)	9808(3)	1755(2)	72(1)	C(58)	13406(8)	4735(5)	1557(3)	115(2)
C(22)	6890(5)	9334(3)	1716(1)	63(1)	C(59)	13219(8)	5126(5)	1232(3)	117(2)
C(23)	3194(4)	10050(3)	1757(1)	45(1)	C(60)	12048(8)	5001(4)	1043(2)	107(2)

Table F3. Bond lengths [Å] and angles [°] for cory121s.

O(1)-C(9)	1.316(5)	C(43)-C(44)	1.464(7)	O(5)-C(23)-O(4)	122.7(4)
O(1)-C(10)	1.459(5)	C(44)-C(46)	1.506(7)	N(2)-C(23)-O(4)	111.9(4)
N(1)-C(11)	1.332(5)	C(46)-C(47)	1.526(8)	O(4)-C(24)-C(25)	109.1(4)
N(1)-C(8)	1.439(5)	C(47)-C(52)	1.345(9)	C(26)-C(25)-C(30)	118.2(5)
C(1)-C(6)	1.377(6)	C(47)-C(48)	1.355(9)	C(26)-C(25)-C(24)	122.0(5)
C(1)-C(2)	1.386(7)	C(48)-C(49)	1.423(10)	C(30)-C(25)-C(24)	119.7(5)
O(2)-C(9)	1.192(4)	C(49)-C(50)	1.374(14)	C(25)-C(26)-C(27)	122.4(6)
N(2)-C(23)	1.330(5)	C(50)-C(51)	1.274(18)	C(28)-C(27)-C(26)	119.6(7)
N(2)-C(16)	1.479(5)	C(51)-C(52)	1.394(13)	C(27)-C(28)-C(29)	121.1(7)
C(2)-C(3)	1.349(8)	C(54)-C(55)	1.497(7)	C(28)-C(29)-C(30)	119.5(7)
O(3)-C(11)	1.242(4)	C(55)-C(56)	1.365(7)	C(25)-C(30)-C(29)	119.2(6)
C(3)-C(4)	1.365(8)	C(55)-C(60)	1.395(8)	C(32)-C(31)-C(36)	122.9(6)
N(3)-C(41)	1.326(6)	C(56)-C(57)	1.385(8)	C(31)-C(32)-C(33)	119.3(6)
N(3)-C(38)	1.443(5)	C(57)-C(58)	1.341(9)	C(34)-C(33)-C(32)	118.9(6)
O(4)-C(23)	1.349(5)	C(58)-C(59)	1.314(9)	C(35)-C(34)-C(33)	121.5(6)
O(4)-C(24)	1.455(5)	C(59)-C(60)	1.409(9)	C(34)-C(35)-C(36)	120.0(6)
C(4)-C(5)	1.392(7)	C(9)-O(1)-C(10)	116.2(4)	C(31)-C(36)-C(35)	117.2(5)
N(4)-C(53)	1.330(6)	C(11)-N(1)-C(8)	124.0(3)	C(31)-C(36)-C(37)	120.1(5)
N(4)-C(46)	1.462(5)	C(6)-C(1)-C(2)	121.0(5)	C(35)-C(36)-C(37)	122.7(5)
O(5)-C(23)	1.210(4)	C(23)-N(2)-C(16)	121.5(4)	C(36)-C(37)-C(38)	113.2(4)
C(5)-C(6)	1.364(6)	C(3)-C(2)-C(1)	120.0(6)	N(3)-C(38)-C(39)	112.3(4)
C(6)-C(7)	1.511(6)	C(2)-C(3)-C(4)	120.3(6)	N(3)-C(38)-C(37)	110.5(4)
O(6)-C(39)	1.323(6)	C(41)-N(3)-C(38)	121.1(4)	C(39)-C(38)-C(37)	112.5(4)
O(6)-C(40)	1.450(7)	C(23)-O(4)-C(24)	114.7(3)	O(7)-C(39)-O(6)	124.4(6)
C(7)-C(8)	1.535(5)	C(3)-C(4)-C(5)	119.3(5)	O(7)-C(39)-C(38)	123.7(6)
O(7)-C(39)	1.203(6)	C(53)-N(4)-C(46)	121.7(4)	O(6)-C(39)-C(38)	111.9(5)
C(8)-C(9)	1.506(6)	C(6)-C(5)-C(4)	121.4(5)	O(8)-C(41)-N(3)	121.0(5)
O(8)-C(41)	1.230(5)	C(5)-C(6)-C(1)	117.8(4)	O(8)-C(41)-C(42)	121.0(4)
O(9)-C(53)	1.354(5)	C(5)-C(6)-C(7)	121.3(4)	N(3)-C(41)-C(42)	117.9(4)
O(9)-C(54)	1.452(5)	C(1)-C(6)-C(7)	120.8(4)	C(41)-C(42)-C(44)	112.5(4)
O(10)-C(53)	1.210(5)	C(39)-O(6)-C(40)	114.2(5)	C(41)-C(42)-C(43)	116.3(5)
C(11)-C(12)	1.496(5)	C(6)-C(7)-C(8)	112.2(3)	C(44)-C(42)-C(43)	58.1(3)
C(12)-C(15)	1.510(5)	N(1)-C(8)-C(9)	111.0(3)	C(41)-C(42)-C(45)	117.6(4)
C(12)-C(14)	1.512(5)	N(1)-C(8)-C(7)	110.5(3)	C(44)-C(42)-C(45)	120.0(5)
C(12)-C(13)	1.512(6)	C(9)-C(8)-C(7)	112.4(3)	C(43)-C(42)-C(45)	118.8(4)
C(13)-C(14)	1.469(6)	O(2)-C(9)-O(1)	124.0(4)	C(44)-C(43)-C(42)	60.9(3)
C(14)-C(16)	1.504(5)	O(2)-C(9)-C(8)	125.4(4)	C(43)-C(44)-C(46)	125.1(4)
C(16)-C(17)	1.512(5)	O(1)-C(9)-C(8)	110.7(4)	C(43)-C(44)-C(42)	61.0(3)
C(17)-C(18)	1.367(5)	C(53)-O(9)-C(54)	116.9(4)	C(46)-C(44)-C(42)	123.1(4)
C(17)-C(22)	1.379(6)	O(3)-C(11)-N(1)	120.8(4)	N(4)-C(46)-C(44)	109.0(4)
C(18)-C(19)	1.373(7)	O(3)-C(11)-C(12)	121.0(3)	N(4)-C(46)-C(47)	112.1(4)
C(19)-C(20)	1.372(7)	N(1)-C(11)-C(12)	118.2(3)	C(44)-C(46)-C(47)	111.4(4)
C(20)-C(21)	1.366(7)	C(11)-C(12)-C(15)	117.6(3)	C(52)-C(47)-C(48)	116.2(7)
C(21)-C(22)	1.375(6)	C(11)-C(12)-C(14)	114.6(3)	C(52)-C(47)-C(46)	119.2(7)
C(24)-C(25)	1.474(6)	C(15)-C(12)-C(14)	120.2(3)	C(48)-C(47)-C(46)	124.6(5)
C(25)-C(26)	1.341(7)	C(11)-C(12)-C(13)	114.5(3)	C(47)-C(48)-C(49)	121.8(8)
C(25)-C(30)	1.385(7)	C(15)-C(12)-C(13)	118.2(4)	C(50)-C(49)-C(48)	118.0(10)
C(26)-C(27)	1.365(9)	C(14)-C(12)-C(13)	58.1(3)	C(51)-C(50)-C(49)	119.8(12)
C(27)-C(28)	1.340(11)	C(14)-C(13)-C(12)	60.9(3)	C(50)-C(51)-C(52)	122.2(14)
C(28)-C(29)	1.340(10)	C(13)-C(14)-C(16)	122.8(3)	C(47)-C(52)-C(51)	121.8(10)
C(29)-C(30)	1.410(8)	C(13)-C(14)-C(12)	60.9(3)	O(10)-C(53)-N(4)	125.9(4)
C(31)-C(32)	1.363(7)	C(16)-C(14)-C(12)	122.4(3)	O(10)-C(53)-O(9)	123.9(4)
C(31)-C(36)	1.363(7)	N(2)-C(16)-C(14)	108.3(3)	N(4)-C(53)-O(9)	110.2(4)
C(32)-C(33)	1.368(9)	N(2)-C(16)-C(17)	111.5(3)	O(9)-C(54)-C(55)	111.5(4)

Table F3. Cont'd

C(33)-C(34)	1.366(8)	C(14)-C(16)-C(17)	113.2(3)	C(56)-C(55)-C(60)	117.0(6)
C(34)-C(35)	1.364(8)	C(18)-C(17)-C(22)	118.0(4)	C(56)-C(55)-C(54)	120.2(5)
C(35)-C(36)	1.390(7)	C(18)-C(17)-C(16)	121.1(4)	C(60)-C(55)-C(54)	122.8(6)
C(36)-C(37)	1.502(7)	C(22)-C(17)-C(16)	120.8(3)	C(55)-C(56)-C(57)	122.0(6)
C(37)-C(38)	1.548(7)	C(17)-C(18)-C(19)	121.2(4)	C(58)-C(57)-C(56)	118.9(7)
C(38)-C(39)	1.500(7)	C(20)-C(19)-C(18)	120.4(5)	C(59)-C(58)-C(57)	122.4(8)
C(41)-C(42)	1.504(7)	C(21)-C(20)-C(19)	119.0(5)	C(58)-C(59)-C(60)	119.7(7)
C(42)-C(44)	1.508(6)	C(20)-C(21)-C(22)	120.3(5)	C(55)-C(60)-C(59)	119.9(7)
C(42)-C(43)	1.509(7)	C(21)-C(22)-C(17)	121.0(4)		
C(42)-C(45)	1.527(7)	O(5)-C(23)-N(2)	125.3(4)		

Table F4. Anisotropic displacement parameters ($Å^2$ x 10^3) for cory121s. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	59(2)	43(2)	110(3)	-7(2)	9(2)	8(2)
N(1)	47(2)	46(2)	31(2)	2(2)	3(2)	13(2)
C(1)	64(3)	68(3)	75(3)	-10(3)	-4(3)	-11(3)
O(2)	58(2)	60(2)	91(2)	-12(2)	11(2)	-12(2)
N(2)	59(2)	42(2)	34(2)	-6(2)	-3(2)	13(2)
C(2)	97(5)	67(4)	127(6)	-30(4)	-11(4)	-9(4)
O(3)	84(2)	72(2)	40(2)	10(2)	6(2)	35(2)
C(3)	88(5)	69(4)	125(6)	19(4)	-28(4)	-19(4)
N(3)	112(3)	52(2)	35(2)	-1(2)	-4(2)	20(2)
O(4)	69(2)	55(2)	43(2)	-2(1)	-13(2)	28(2)
C(4)	59(4)	97(4)	88(4)	35(4)	-10(3)	-23(3)
N(4)	95(3)	55(3)	38(2)	6(2)	8(2)	6(2)
O(5)	77(2)	66(2)	43(2)	-12(2)	-7(2)	27(2)
C(5)	52(3)	70(3)	69(3)	3(2)	3(3)	-6(3)
C(6)	34(2)	54(3)	52(3)	5(2)	-13(2)	4(2)
O(6)	91(3)	86(3)	105(3)	0(2)	-19(2)	20(2)
C(7)	47(3)	52(3)	56(3)	5(2)	-1(2)	7(2)
O(7)	173(4)	69(3)	99(3)	37(2)	3(3)	15(3)
C(8)	41(2)	47(2)	36(2)	6(2)	5(2)	7(2)
O(8)	124(3)	72(2)	39(2)	1(2)	-1(2)	16(2)
C(9)	40(3)	52(3)	45(2)	-4(2)	3(2)	-4(2)
O(9)	88(2)	63(2)	50(2)	12(2)	3(2)	18(2)
C(10)	80(4)	40(3)	152(5)	-12(3)	-7(4)	-2(3)
O(10)	104(3)	75(2)	46(2)	-4(2)	11(2)	20(2)
C(11)	41(2)	43(2)	31(2)	4(2)	3(2)	-2(2)
C(12)	38(2)	47(2)	39(2)	9(2)	-3(2)	4(2)
C(13)	46(3)	47(3)	77(3)	-5(2)	-2(2)	7(2)
C(14)	41(2)	42(2)	40(2)	2(2)	-1(2)	11(2)
C(15)	80(4)	67(3)	39(2)	5(2)	7(2)	35(3)
C(16)	52(3)	40(2)	31(2)	7(2)	-5(2)	5(2)
C(17)	48(3)	35(2)	43(2)	6(2)	-4(2)	3(2)
C(18)	61(3)	58(3)	54(3)	-10(2)	-8(2)	4(3)
C(19)	85(4)	62(3)	62(3)	-11(3)	-19(3)	-4(3)
C(20)	66(4)	64(3)	92(4)	7(3)	-7(3)	-21(3)
C(21)	67(4)	75(4)	75(4)	0(3)	9(3)	-11(3)
C(22)	64(3)	65(3)	59(3)	-11(2)	-1(3)	-12(3)
C(23)	47(3)	45(3)	42(3)	-7(2)	0(2)	7(2)
C(24)	115(5)	79(4)	65(3)	-10(3)	-22(3)	58(3)
C(25)	59(3)	49(3)	55(3)	-9(2)	-2(3)	16(2)
C(26)	86(4)	75(4)	89(4)	5(3)	21(4)	21(3)
C(27)	181(9)	95(5)	76(5)	21(4)	23(5)	55(6)
C(28)	207(11)	95(5)	81(5)	-3(4)	-39(6)	89(7)
C(29)	81(5)	87(5)	156(7)	-14(5)	-56(5)	23(4)
C(30)	86(5)	54(3)	95(4)	5(3)	7(3)	1(3)
C(31)	93(4)	69(4)	94(4)	-2(3)	-20(3)	-15(3)
C(32)	115(5)	106(5)	82(4)	-9(4)	-22(4)	-16(4)
C(33)	121(6)	102(6)	105(6)	-25(4)	-6(4)	-9(4)
C(34)	153(7)	68(4)	120(6)	-13(4)	-3(5)	-2(4)
C(35)	138(6)	58(4)	94(4)	11(3)	9(4)	-4(4)
C(36)	62(3)	60(3)	81(4)	2(3)	8(3)	-7(3)
C(37)	76(4)	70(4)	102(4)	-3(3)	15(3)	-2(3)

Table F4. Cont'd

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(38)	81(4)	50(3)	52(3)	0(2)	8(2)	10(3)
C(39)	104(5)	61(4)	54(3)	1(3)	6(3)	8(3)
C(40)	156(7)	154(7)	148(7)	-34(5)	-81(6)	64(6)
C(41)	93(4)	56(3)	46(3)	2(2)	-7(2)	-4(3)
C(42)	124(5)	52(3)	48(3)	-7(2)	-26(3)	23(3)
C(43)	111(5)	46(3)	123(5)	8(3)	-33(4)	-6(3)
C(44)	92(4)	52(3)	37(2)	6(2)	-8(3)	-3(3)
C(45)	291(11)	110(5)	44(3)	-33(3)	-42(5)	110(6)
C(46)	102(4)	53(3)	37(3)	1(2)	9(2)	5(3)
C(47)	101(5)	52(3)	72(4)	1(3)	30(3)	-1(3)
C(48)	170(9)	156(7)	74(4)	15(4)	-29(5)	-81(6)
C(49)	231(11)	201(10)	76(5)	5(6)	-21(6)	-138(9)
C(50)	265(15)	133(9)	145(8)	-67(7)	105(10)	-95(11)
C(51)	173(12)	84(7)	500(30)	7(10)	95(14)	-32(9)
C(52)	113(7)	82(6)	388(16)	47(7)	40(8)	-5(5)
C(53)	72(3)	59(3)	37(3)	-7(2)	1(2)	4(3)
C(54)	95(4)	55(3)	76(3)	-5(3)	1(3)	12(3)
C(55)	79(4)	46(3)	81(4)	-2(3)	11(3)	18(3)
C(56)	85(4)	83(4)	86(4)	-3(3)	0(3)	15(3)
C(57)	111(6)	106(5)	96(5)	-11(4)	-15(5)	24(5)
C(58)	103(6)	82(5)	161(8)	-26(5)	-4(6)	9(5)
C(59)	107(6)	78(5)	166(8)	14(5)	4(6)	-18(4)
C(60)	124(6)	71(4)	126(6)	13(4)	9(5)	1(4)

Table F5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for cory121s.

	x	y	z	U(eq)		x	y	z	U(eq)
H(1N)	6710(30)	6040(20)	2350(10)	31(11)	H(28)	-451	12361	356	153
H(1)	8629	6971	2615	83	H(29)	-1629	11845	843	129
H(2N)	4000(30)	9170(20)	1444(10)	32(11)	H(30)	-588	11266	1374	94
H(2)	9302	8443	2533	116	H(31A)	5645	10598	1171	102
H(3)	10596	8808	2043	113	H(32A)	5466	11618	1645	121
H(3N)	4780(40)	9090(30)	85(12)	52(13)	H(33A)	5195	13132	1508	131
H(4)	11377	7694	1658	97	H(34A)	5141	13582	895	136
H(4N)	7680(40)	6290(30)	1125(13)	68(15)	H(35A)	5266	12555	420	116
H(5)	10643	6226	1727	76	H(37A)	6283	10339	506	99
H(7A)	8941	5360	2489	62	H(37B)	5783	11035	210	99
H(7B)	9746	5061	2139	62	H(38A)	3906	10168	639	73
H(8)	8028	5452	1743	50	H(40A)	809	10028	-235	229
H(10A)	7782	2665	2204	136	H(40B)	1917	10546	-440	229
H(10B)	8795	2489	1888	136	H(40C)	1184	11007	-108	229
H(10C)	7370	2709	1782	136	H(43A)	4619	7016	872	112
H(13A)	3803	6717	1731	68	H(43B)	5346	6386	562	112
H(13B)	3309	7314	2088	68	H(44A)	6459	7824	982	73
H(14)	5231	7840	1560	49	H(45A)	6100	8264	-66	223
H(15A)	5328	6835	2632	93	H(45B)	5227	7403	-86	223
H(15B)	4950	7846	2561	93	H(45C)	6678	7309	21	223
H(15C)	6390	7548	2535	93	H(46A)	7822	6898	409	77
H(16)	4266	8850	2180	49	H(48A)	10176	7158	981	160
H(18)	5566	9896	2487	69	H(49A)	11682	8339	1020	203
H(19)	7444	10681	2557	83	H(50A)	11143	9737	772	217
H(20)	8981	10646	2094	88	H(51A)	9317	9908	479	304
H(21)	8635	9781	1569	87	H(52A)	7797	8786	466	233
H(22)	6761	8984	1503	75	H(54A)	9957	4217	747	90
H(24A)	2456	11699	1621	104	H(54B)	9457	3741	1111	90
H(24B)	1249	11125	1734	104	H(56A)	10774	3666	1640	102
H(26)	2741	11890	910	100	H(57A)	12697	3912	1943	125
H(27)	1717	12406	389	141					

Appendix G

X-ray crystal data for 408

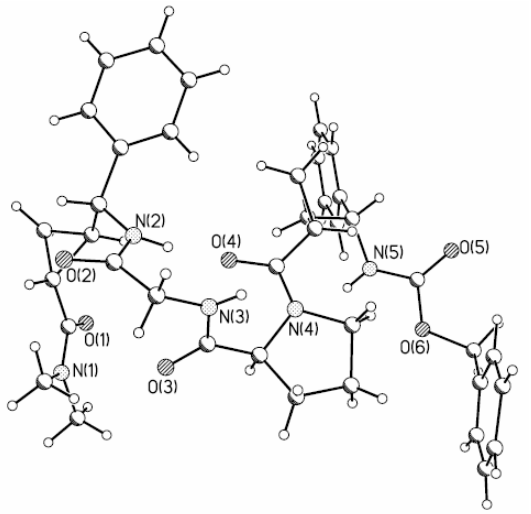


Table G1. Crystal data and structure refinement for CORY903.

Identification code	cory903	
Empirical formula	$C_{39}H_{45}N_5O_6$	
Formula weight	679.80	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 11.475(2) Å	α= 90°.
	b = 12.1310(10) Å	β= 94.809(4)°.
	c = 13.299(2) Å	γ = 90°.
Volume	1844.7(5) $Å^3$	
Z	2	
Density (calculated)	1.224 Mg/m^3	
Absorption coefficient	0.083 mm^{-1}	
F(000)	724	
Crystal size	0.11 x 0.11 x 0.21 mm^3	
Theta range for data collection	1.54 to 32.60°.	
Index ranges	-17<=h<=16, -18<=k<=18, -19<=l<=19	
Reflections collected	22963	
Independent reflections	12339 [R(int) = 0.0769]	
Completeness to theta = 32.60°	95.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	12339 / 1 / 457	
Goodness-of-fit on F^2	0.916	
Final R indices [I>2sigma(I)]	R1 = 0.0729, wR2 = 0.1562	
R indices (all data)	R1 = 0.1672, wR2 = 0.1986	
Absolute structure parameter	-0.3(13)	
Largest diff. peak and hole	0.364 and -0.212 $e.Å^{-3}$	

Table G2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for CORY903. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	8874(3)	5637(2)	7403(2)	51(1)
O(1)	7737(2)	4834(2)	6164(2)	61(1)
C(1)	9351(4)	6608(3)	7949(3)	61(1)
O(2)	8865(2)	9411(2)	6683(2)	46(1)
N(2)	8774(2)	8493(2)	5208(2)	36(1)
C(2)	9486(4)	4593(4)	7614(3)	77(1)
O(3)	10975(2)	6975(2)	6228(2)	56(1)
N(3)	11189(2)	8445(2)	5234(2)	37(1)
C(3)	8031(3)	5668(3)	6654(3)	46(1)
O(4)	9698(2)	6879(2)	3794(1)	40(1)
N(4)	11641(2)	6906(2)	3657(2)	37(1)
C(4)	7430(3)	6725(3)	6441(2)	50(1)
N(5)	10853(2)	4668(3)	1170(2)	47(1)
O(5)	11804(3)	4830(3)	-243(2)	90(1)
C(5)	6249(3)	6738(4)	5843(3)	65(1)
C(6)	7294(2)	7117(3)	5357(2)	44(1)
O(6)	12558(2)	3877(3)	1135(2)	80(1)
C(7)	7520(2)	8306(3)	5159(2)	40(1)
C(8)	9356(2)	9020(2)	5984(2)	34(1)
C(9)	10654(2)	9163(3)	5943(2)	43(1)
C(10)	11305(2)	7371(3)	5462(2)	38(1)
C(11)	11899(2)	6651(2)	4733(2)	37(1)
C(12)	13235(2)	6757(3)	4878(3)	50(1)
C(13)	13612(3)	6338(3)	3870(3)	56(1)
C(14)	12696(3)	6787(3)	3102(3)	53(1)
C(15)	10528(2)	6902(2)	3256(2)	37(1)
C(16)	10313(3)	6887(3)	2133(2)	46(1)
C(17)	9137(3)	7185(3)	1633(3)	59(1)
C(18)	9501(3)	6005(3)	1712(2)	43(1)
C(19)	9852(3)	5332(3)	835(2)	45(1)
C(20)	11728(3)	4494(4)	610(3)	60(1)
C(21)	13693(3)	3706(5)	690(3)	122(2)
C(22)	14644(3)	4354(5)	1378(3)	128(3)
C(23)	15389(3)	3798(5)	2083(3)	187(5)
C(24)	16222(12)	4100(30)	2587(14)	370(20)
C(25)	16383(10)	5360(20)	2583(11)	288(14)
C(26)	15648(9)	6105(10)	1807(9)	194(5)
C(27)	14783(9)	5517(9)	1231(8)	164(3)
C(28)	5711(3)	8838(3)	4058(3)	57(1)
C(29)	5134(3)	9222(3)	3182(4)	70(1)
C(30)	5782(4)	9542(5)	2396(4)	95(2)
C(31)	6948(4)	9464(6)	2485(3)	111(2)
C(32)	7522(3)	9079(5)	3381(3)	95(2)
C(33)	6916(2)	8746(3)	4166(2)	45(1)
C(34)	8794(4)	3551(4)	423(3)	77(1)
C(35)	7800(5)	2989(5)	-2(4)	98(2)
C(36)	6927(4)	3512(6)	-507(4)	98(2)
C(37)	6967(4)	4626(6)	-577(4)	106(2)
C(38)	7909(4)	5214(4)	-152(3)	78(1)
C(39)	8834(3)	4663(3)	362(2)	47(1)

Table G3. Bond lengths [Å] and angles [°] for CORY903.

N(1)-C(3)	1.329(4)	C(28)-C(33)	1.383(4)	C(11)-C(12)-C(13)	102.5(3)
N(1)-C(1)	1.466(5)	C(29)-C(30)	1.389(7)	C(14)-C(13)-C(12)	104.0(3)
N(1)-C(2)	1.464(5)	C(30)-C(31)	1.336(6)	N(4)-C(14)-C(13)	104.6(3)
O(1)-C(3)	1.235(4)	C(31)-C(32)	1.393(6)	O(4)-C(15)-N(4)	121.5(2)
O(2)-C(8)	1.223(3)	C(32)-C(33)	1.363(5)	O(4)-C(15)-C(16)	120.4(3)
N(2)-C(8)	1.342(4)	C(34)-C(39)	1.353(6)	N(4)-C(15)-C(16)	118.0(2)
N(2)-C(7)	1.453(4)	C(34)-C(35)	1.406(6)	C(15)-C(16)-C(18)	115.4(3)
O(3)-C(10)	1.215(3)	C(35)-C(36)	1.321(8)	C(15)-C(16)-C(17)	120.6(3)
N(3)-C(10)	1.342(4)	C(36)-C(37)	1.356(8)	C(18)-C(16)-C(17)	59.8(2)
N(3)-C(9)	1.457(4)	C(37)-C(38)	1.376(6)	C(18)-C(17)-C(16)	60.1(2)
C(3)-C(4)	1.472(5)	C(38)-C(39)	1.385(5)	C(17)-C(18)-C(16)	60.2(2)
O(4)-C(15)	1.239(3)	C(3)-N(1)-C(1)	124.5(3)	C(17)-C(18)-C(19)	123.9(3)
N(4)-C(15)	1.341(4)	C(3)-N(1)-C(2)	118.4(3)	C(16)-C(18)-C(19)	118.6(3)
N(4)-C(11)	1.470(4)	C(1)-N(1)-C(2)	116.6(3)	N(5)-C(19)-C(18)	108.7(2)
N(4)-C(14)	1.477(4)	C(8)-N(2)-C(7)	122.4(2)	N(5)-C(19)-C(39)	113.3(3)
C(4)-C(6)	1.513(5)	C(10)-N(3)-C(9)	118.2(3)	C(18)-C(19)-C(39)	111.4(3)
C(4)-C(5)	1.512(5)	O(1)-C(3)-N(1)	121.4(3)	O(5)-C(20)-N(5)	126.3(4)
N(5)-C(20)	1.317(4)	O(1)-C(3)-C(4)	120.6(3)	O(5)-C(20)-O(6)	124.3(4)
N(5)-C(19)	1.442(4)	N(1)-C(3)-C(4)	118.0(3)	N(5)-C(20)-O(6)	109.4(3)
O(5)-C(20)	1.215(4)	C(15)-N(4)-C(11)	119.6(2)	O(6)-C(21)-C(22)	106.6(2)
C(5)-C(6)	1.482(5)	C(15)-N(4)-C(14)	126.5(2)	C(23)-C(22)-C(27)	120.0(5)
C(6)-C(7)	1.493(5)	C(11)-N(4)-C(14)	111.0(2)	C(23)-C(22)-C(21)	120.4
O(6)-C(20)	1.357(5)	C(3)-C(4)-C(6)	117.8(3)	C(27)-C(22)-C(21)	119.5(5)
O(6)-C(21)	1.489(4)	C(3)-C(4)-C(5)	119.7(3)	C(24)-C(23)-C(22)	130.8(15)
C(7)-C(33)	1.536(4)	C(6)-C(4)-C(5)	58.6(2)	C(23)-C(24)-C(25)	114(2)
C(8)-C(9)	1.505(4)	C(20)-N(5)-C(19)	122.6(3)	C(26)-C(25)-C(24)	121.2(15)
C(10)-C(11)	1.508(4)	C(6)-C(5)-C(4)	60.7(2)	C(27)-C(26)-C(25)	112.6(12)
C(11)-C(12)	1.534(4)	C(5)-C(6)-C(7)	122.4(3)	C(26)-C(27)-C(22)	120.6(10)
C(12)-C(13)	1.529(5)	C(5)-C(6)-C(4)	60.7(2)	C(29)-C(28)-C(33)	121.5(4)
C(13)-C(14)	1.505(5)	C(7)-C(6)-C(4)	117.8(3)	C(30)-C(29)-C(28)	118.9(3)
C(15)-C(16)	1.493(4)	C(20)-O(6)-C(21)	118.1(3)	C(31)-C(30)-C(29)	120.6(4)
C(16)-C(18)	1.496(4)	N(2)-C(7)-C(6)	109.3(2)	C(30)-C(31)-C(32)	119.9(5)
C(16)-C(17)	1.497(5)	N(2)-C(7)-C(33)	111.0(2)	C(33)-C(32)-C(31)	121.3(4)
C(17)-C(18)	1.491(5)	C(6)-C(7)-C(33)	114.5(3)	C(32)-C(33)-C(28)	117.8(3)
C(18)-C(19)	1.507(4)	O(2)-C(8)-N(2)	122.5(2)	C(32)-C(33)-C(7)	122.7(3)
C(19)-C(39)	1.516(4)	O(2)-C(8)-C(9)	120.2(3)	C(28)-C(33)-C(7)	119.5(3)
C(21)-C(22)	1.5741	N(2)-C(8)-C(9)	117.2(2)	C(39)-C(34)-C(35)	119.3(5)
C(22)-C(23)	1.39	N(3)-C(9)-C(8)	115.3(2)	C(36)-C(35)-C(34)	121.8(5)
C(22)-C(27)	1.435(11)	O(3)-C(10)-N(3)	122.8(3)	C(35)-C(36)-C(37)	119.0(5)
C(23)-C(24)	1.181(16)	O(3)-C(10)-C(11)	119.9(3)	C(38)-C(37)-C(36)	121.3(5)
C(24)-C(25)	1.53(3)	N(3)-C(10)-C(11)	117.3(3)	C(37)-C(38)-C(39)	119.7(5)
C(25)-C(26)	1.57(2)	N(4)-C(11)-C(10)	116.0(2)	C(34)-C(39)-C(38)	118.9(4)
C(26)-C(27)	1.396(13)	N(4)-C(11)-C(12)	102.8(2)	C(34)-C(39)-C(19)	122.5(3)
C(28)-C(29)	1.372(6)	C(10)-C(11)-C(12)	111.8(2)	C(38)-C(39)-C(19)	118.6(3)

Table G4. Anisotropic displacement parameters ($Å^2$ x 10^3) for CORY903. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	63(2)	45(2)	46(2)	-1(1)	8(1)	10(1)
O(1)	57(1)	60(2)	68(2)	-7(1)	5(1)	2(1)
C(1)	88(3)	53(2)	42(2)	0(2)	0(2)	4(2)
O(2)	51(1)	55(1)	32(1)	-6(1)	5(1)	6(1)
N(2)	30(1)	42(1)	36(1)	-5(1)	0(1)	7(1)
C(2)	99(3)	66(3)	64(2)	2(2)	-11(2)	27(2)
O(3)	67(1)	56(2)	48(1)	9(1)	14(1)	11(1)
N(3)	36(1)	39(1)	37(1)	-7(1)	1(1)	-3(1)
C(3)	46(2)	50(2)	46(2)	-2(2)	17(2)	-2(2)
O(4)	33(1)	45(1)	41(1)	-6(1)	0(1)	-1(1)
N(4)	33(1)	44(1)	33(1)	-2(1)	5(1)	-4(1)
C(4)	53(2)	57(2)	42(2)	-4(2)	13(1)	7(2)
N(5)	46(2)	68(2)	29(1)	-4(1)	5(1)	-4(1)
O(5)	105(2)	123(3)	46(2)	3(2)	35(2)	12(2)
C(5)	41(2)	72(3)	81(3)	10(2)	6(2)	0(2)
C(6)	33(1)	56(2)	42(2)	-4(2)	3(1)	-1(1)
O(6)	63(2)	112(2)	67(2)	-7(2)	14(1)	19(2)
C(7)	28(1)	52(2)	40(2)	-12(1)	6(1)	7(1)
C(8)	33(1)	35(2)	32(1)	5(1)	-3(1)	6(1)
C(9)	38(2)	45(2)	44(2)	-11(1)	-3(1)	2(1)
C(10)	28(1)	46(2)	39(2)	0(1)	-1(1)	0(1)
C(11)	33(1)	38(2)	38(2)	3(1)	-5(1)	1(1)
C(12)	33(1)	56(2)	59(2)	-4(2)	1(1)	1(2)
C(13)	40(2)	59(2)	72(3)	-7(2)	17(2)	-4(2)
C(14)	45(2)	63(2)	52(2)	-4(2)	14(2)	-9(2)
C(15)	43(2)	31(1)	35(1)	-7(1)	0(1)	-5(1)
C(16)	55(2)	45(2)	39(2)	1(2)	5(1)	-7(2)
C(17)	75(2)	55(2)	44(2)	3(2)	-14(2)	5(2)
C(18)	43(2)	52(2)	34(2)	1(1)	-4(1)	-1(1)
C(19)	49(2)	54(2)	30(2)	1(1)	-2(1)	-6(2)
C(20)	61(2)	75(3)	44(2)	-12(2)	5(2)	-3(2)
C(21)	108(4)	145(5)	121(5)	-18(4)	65(4)	27(4)
C(22)	44(2)	264(10)	81(4)	25(5)	23(2)	37(4)
C(23)	101(5)	299(13)	169(8)	68(9)	54(5)	18(7)
C(24)	85(7)	830(60)	193(14)	130(30)	-28(7)	-98(19)
C(25)	68(6)	660(40)	135(10)	-103(18)	9(6)	29(13)
C(26)	138(8)	243(12)	211(11)	-92(10)	84(8)	-52(8)
C(27)	156(8)	177(8)	165(8)	2(7)	44(7)	4(7)
C(28)	41(2)	54(2)	73(2)	1(2)	-9(2)	3(2)
C(29)	39(2)	70(2)	96(3)	-9(2)	-30(2)	10(2)
C(30)	73(3)	142(5)	65(3)	-1(3)	-25(2)	33(3)
C(31)	72(3)	204(7)	57(3)	30(3)	-4(2)	44(4)
C(32)	49(2)	189(6)	47(2)	21(3)	7(2)	39(3)
C(33)	34(1)	56(2)	46(2)	-6(2)	-4(1)	7(1)
C(34)	71(3)	78(3)	78(3)	-15(2)	-11(2)	-12(2)
C(35)	92(4)	86(4)	116(4)	-42(3)	8(3)	-30(3)
C(36)	61(3)	137(5)	94(4)	-64(4)	-3(3)	-19(3)
C(37)	74(3)	135(5)	101(4)	-26(4)	-38(3)	-5(3)
C(38)	66(3)	92(3)	71(3)	-4(2)	-22(2)	0(2)
C(39)	48(2)	63(2)	30(1)	-6(2)	1(1)	-7(2)

Table G5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for CORY903.

	x	y	z	U(eq)
H(1A)	8890	7260	7733	92
H(1B)	10166	6717	7804	92
H(1C)	9314	6497	8676	92
H(2N)	9260(20)	8120(20)	4810(19)	16(6)
H(2A)	9106	4009	7196	116
H(2B)	9459	4406	8329	116
H(2C)	10302	4666	7459	116
H(3N)	11580(30)	8800(30)	4760(30)	44(9)
H(4A)	7566	7310	6967	60
H(5N)	10820(30)	4500(30)	1750(30)	67(12)
H(5A)	5903	6020	5626	77
H(5B)	5678	7302	6020	77
H(6A)	7586	6593	4855	52
H(7A)	7211	8737	5720	48
H(9A)	10810	9938	5763	51
H(9B)	11040	9030	6626	51
H(11A)	11682	5866	4851	44
H(12A)	13565	6297	5446	60
H(12B)	13476	7533	4999	60
H(13A)	14398	6619	3748	68
H(13B)	13626	5522	3854	68
H(14A)	12940	7508	2842	63
H(14B)	12552	6270	2529	63
H(16A)	11001	7051	1744	55
H(17A)	8533	7441	2068	71
H(17B)	9109	7537	960	71
H(18A)	9115	5573	2232	52
H(19A)	10100	5855	311	54
H(21A)	13650	3992	-10	146
H(21B)	13888	2912	678	146
H(23A)	15195	3045	2175	225
H(24A)	16744	3618	2959	447
H(25A)	16940	5686	3060	346
H(26A)	15775	6873	1736	232
H(27A)	14284	5891	737	197
H(28A)	5272	8631	4603	68
H(29A)	4304	9269	3115	84
H(30A)	5393	9817	1789	114
H(31A)	7384	9672	1939	134
H(32A)	8352	9048	3446	114
H(34A)	9431	3153	750	92
H(35A)	7755	2212	77	118
H(36A)	6281	3113	-817	117
H(37A)	6333	5008	-926	127
H(38A)	7925	5994	-211	93

Appendix H

Temperature shift coefficient plots for peptides 392, 411, 415, 421, 422 and 426

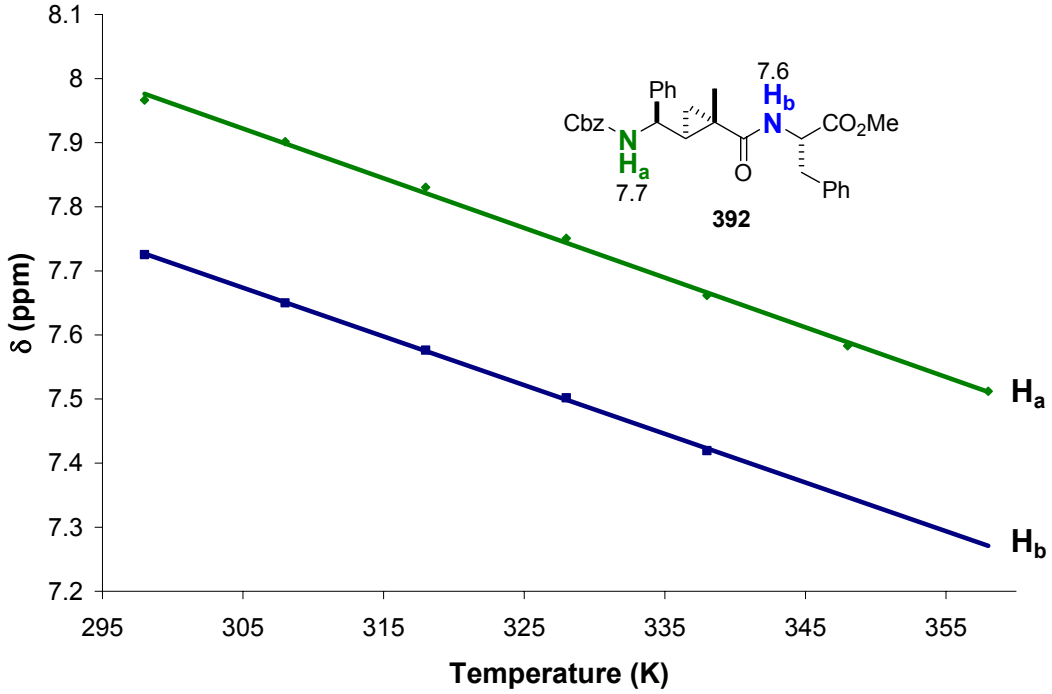


Figure H.1. Amide proton chemical shift dependence on temperature for a 5.0 mM solution of tetraapeptide **392** in DMSO-d_6

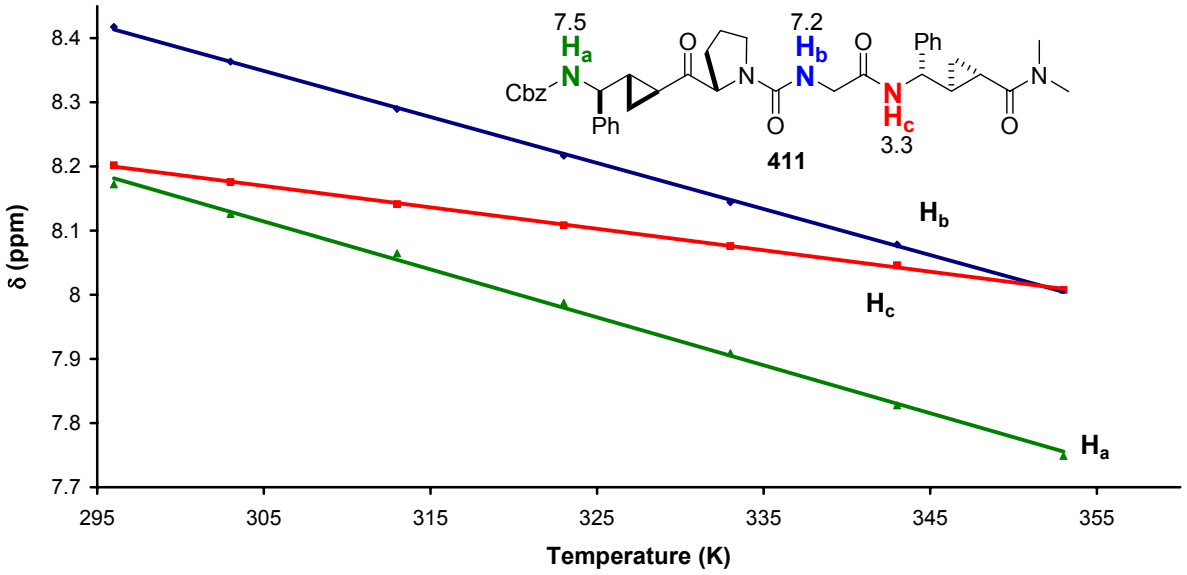


Figure H.2. Amide proton chemical shift dependence on temperature for a 5.0 mM solution of tetraapeptide **411** in DMSO-d_6

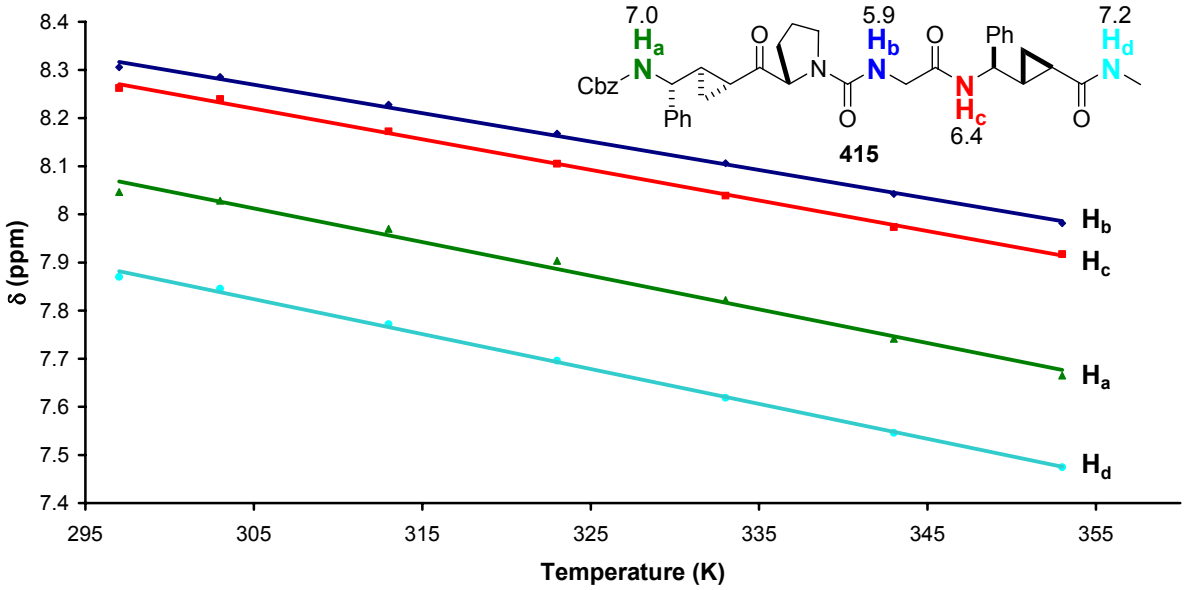


Figure H.3. Amide proton chemical shift dependence on temperature for a 5.0 mM solution of tetraapeptide **415** in DMSO-d_6

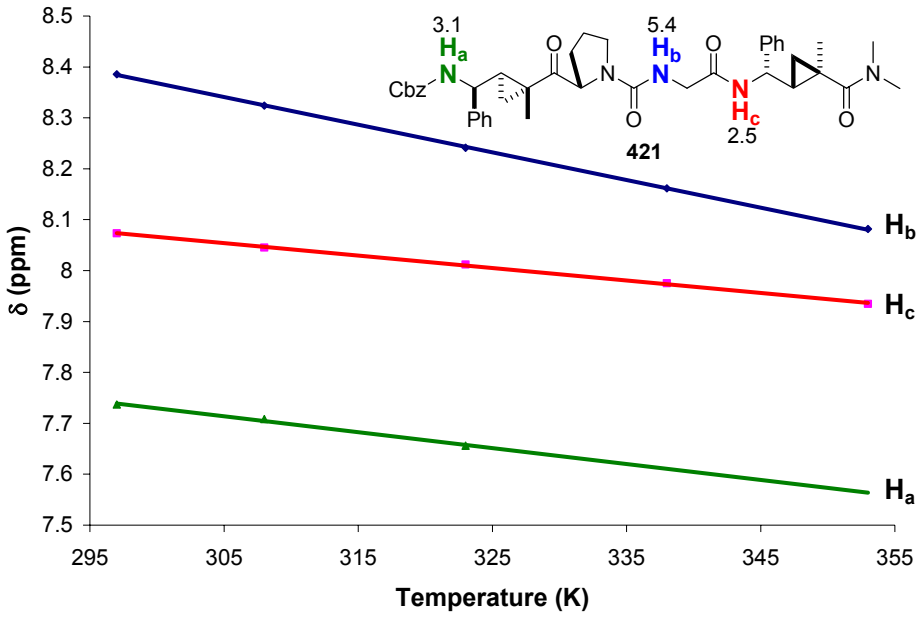


Figure H.4. Amide proton chemical shift dependence on temperature for a 5.0 mM solution of tetraapeptide **421** in DMSO-d_6

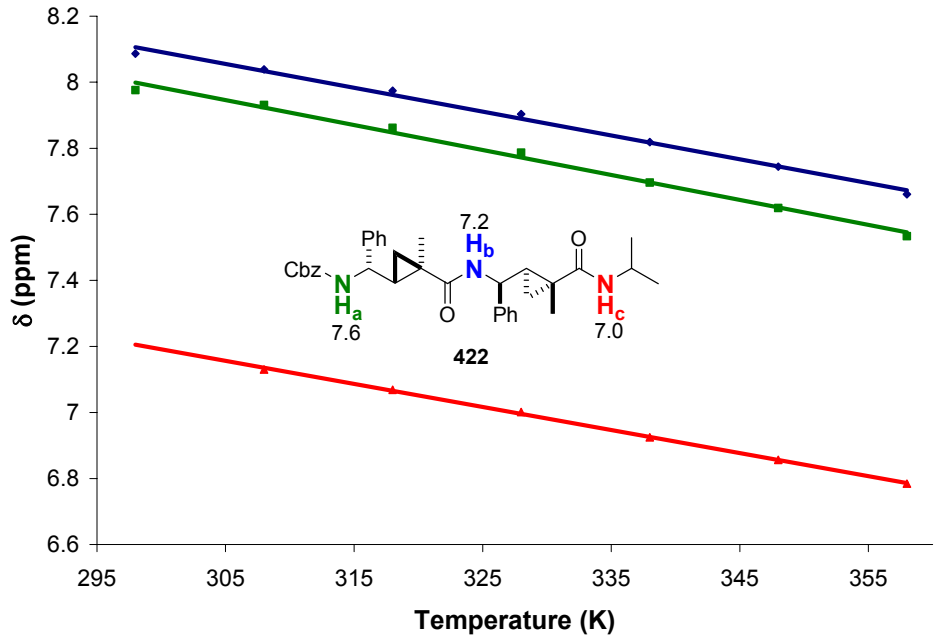


Figure H.5. Amide proton chemical shift dependence on temperature for a 5.0 mM solution of tetraapeptide **422** in DMSO-d_6

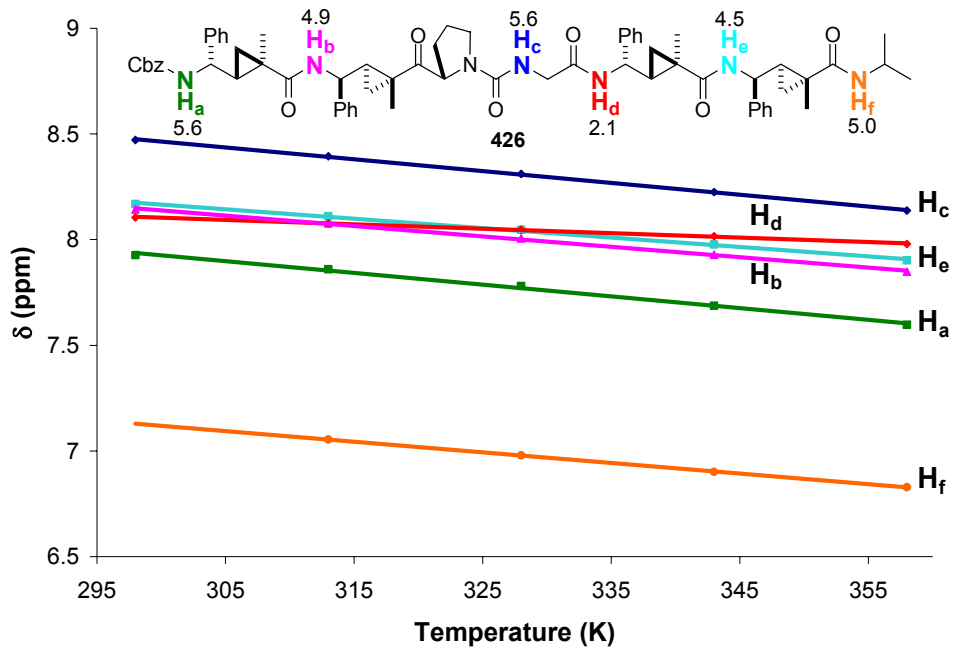


Figure H.6. Amide proton chemical shift dependence on temperature for a 5.0 mM solution of tetraapeptide **426** in DMSO-d_6

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156. Lowering the reaction temperature to -40 °C did not improve the diastereoselection and the reaction did not proceed at -78 °C, possibly due to the formation of precipitates.
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184. Traces of alkene containing products were removed by treatment of the crude reaction mixture with OsO_4/NMO.
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272. The pK_a of *o*-$NO_2C_6H_4SeOH$ has been measured to be 10.45 (ref. 272b) while $PhSeO_2H$ has a measured pK_a of 4.79 (ref. 272a). The pK_a of PhSeOH has been approximated to be ~11.5 (ref. 272b). On the basis of this approximation, the pK_a of *o*-$NO_2C_6H_4SeO_2H$ can be estimated to be ~3.8. *Cf.* (a) McCullogh, J. D.; Gould, E. S. *J. Am. Chem. Soc.* **1949**, *71*, 674. (b) Kang, S.-I.; Kice, J. L. *J. Org. Chem.* **1986**, *51*, 287.
273. Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831.
274. A library of allylic and *C*-cyclopropylalkylamides prepared during the development of the methodologies described in Chapter 1 was evaluated for anti-estrogenic activity in collaboration with Professor Billy Day. An interesting lead structure prepared by Dr. Chris Kendall was discovered amongst the compounds. A preliminary communication detailing these efforts has recently been published. Janjic, J. M.; Mu, Y.; Kendall, C.; Stephenson, C. R. J.; Balachandran, B.; Raccor, B. S.; Lu, Y.; Zhu, G.; Xie, W.; Wipf, P.; Day, B. W. *Biorg. Med. Chem.* **2005**, *13*, 157.
275. This work has been carried out in collaboration with Prof. Kristen Lynch at the University of Texas, Southwestern Medical Center at Dallas.
276. See Appendix B for crystal coordinates.
277. Crystals suitable for x-ray diffraction studies were obtained from slow evaporation of a solution of **372** in CH_2Cl_2 and toluene (ca. 3 drops).
278. Indeed, peptide mimetics with an extra carbon atom in the backbone sequence have been prepared by Mr. Jingbo Xiao and β-turn motifs have been observed. For example, see Wipf, P.; Xiao, J. *Org. Lett*. **2005**, *7*, 103.
279. See Appendix C for crystal coordinates.

280. Wipf, P.; Nunes, R. L.; Ribe, S. *Helv. Chim. Acta* **2002**, *85*, 3478.
281. Ribe, S. D. Ph.D Dissertation, University of Pittsburgh, 2003.
282. $Zn(CH_2I)_2$ has been reported as an explosion hazard and the DME complex is suggested as a safe alternative for reactions run using ≥1 mmol of reagent. For the original report, see Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081.
283. Mu, Y.; Stephenson, C. R. J.; Kendall, C.; Saini, S. P. S.; Toma, D.; Ren, S.; Cai, H.; Strom, S. C.; Day, B. W.; Wipf, P.; Xie, W. *Submitted to Mol. Pharm.*
284. See Appendix D for crystal coordinates.
285. For a stimulating discussion of the attempted solutions to this problem, see Kendall, C., Ph.D Dissertation, University of Pittsburgh, 2004.
286. Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*, Wiley, New York, 1981.
287. The resolution was not optimized, and it is expected optimization of the acid could improve the recovery.
288. See experimental section for details.
289. Attempts to obtain crystals suitable for x-ray diffraction analysis from **383**, **384**, **385** and **386** were unsuccessful.
290. HPLC conditions: Microsorb-MV 100 column, 3:1 hexanes/EtOAc, **388** 13.2 min; **389** 10.8 min.
291. For the use of x-ray for the determination of absolute stereochemistry using heavy atoms, see Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876.
292. LiOH mediated saponifications are slow at r.t. and reagents which require warming above r.t. lead to the formation of unidentified side products.
293. HPLC conditions: Microsorb-MV 100 column, 7:3 hexanes/EtOAc, **392** 4.5 min; **391** 5.9 min.
294. See Appendix E for crystal coordinates.
295. We were able to grow crystals suitable for x-ray diffraction analysis from a mixture of hexanes and ethyl acetate.
296. See Appendix F for crystal coordinates.
297. Similarly, attempts to recrystallize this material were unsuccessful.
298. See Appendix G for crystal coordinates.

299. We have been able to grow crystals of **426** from CH_2Cl_2/toluene and EtOAc/hexanes, however, the structure could not be solved.
300. A Monte-Carlo search routine was used to find the lowest energy conformations and only those within 5 kJ/mol of the lowest energy conformer were included in the overlay representations for all the peptides presented herein. For **388**, **389**, **391**, **392**, **397**, **408**, **411**, **415**, **421** and **422**, 10,000 conformations were analyzed. In the case of **426**, 25,000 structures were analyzed.
301. For both **388** and **389**, the lowest energy conformation is the pseudo-β-turn.
302. For the interpretation of temperature shift coefficients in polar aprotic solvents such as DMSO-d_6, see Smith, J. A.; Pease, L. G. *Crit. Rev. Bioch.* **1980**, *8*, 315.
303. For the interpretation of temperature shift coefficients in non-polar solvents such as $CDCl_3$, see Stevens, E. S.; Sugawara, N.; Bonora, G. M.; Toniolo, C. *J. Am. Chem. Soc.* **1980**, *102*, 7048.
304. Imperiali, B.; Fisher, S. L.; Moats, R. A.; Prins, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 3182.
305. The residue number was assigned on the basis of the β-turn where the Pro residue is i+1, Gly i+2, etc.
306. Circular dichroism spectra were measured for a 0.2 mM solution in MeOH. Shown are 5 averaged scans at 21 °C.
307. $Zn(CH_2I)_2$•DME complex was prepared by dropwise addition of CH_2I_2 (0.72 mL, 8.9 mmol) to a cooled (-20 °C) solution of Et_2Zn (0.55 g, 4.5 mmol) and DME (0.46 mL, 4.5 mmol) in dry CH_2Cl_2 (2.5 mL). The solution was stirred for 10 min and added to the reaction mixture via canula.
308. Tri-*n*-butylphosphine was stored in a glove box.