Published in final edited form as:
Org Process Res Dev. 2012 ; 16(1): 26–34. doi:10.1021/op2002613.

Allylic Amines as Key Building Blocks in the Synthesis of (*E*)-Alkene Peptide Isosteres

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Abstract

Nucleophilic imine additions with vinyl organometallics have developed into efficient, high yielding, and robust methodologies to generate structurally diverse allylic amines. We have used the hydrozirconation-transmetalation-imine addition protocol in the synthesis of allylic amine intermediates for peptide bond isosteres, phosphatase inhibitors, and mitochondria-targeted peptide mimetics. The gramicidin S-derived XJB-5-131 and JP4-039 and their analogs have been prepared on up to 160 g scale for preclinical studies. These (*E*)-alkene peptide isosteres adopt type II′ β-turn secondary structures and display impressive biological properties, including selective reactions with reactive oxygen species (ROS) and prevention of apoptosis.

Keywords

Imine additions; allylic amines; alkene peptide isosteres; mitochondrial targeting; gramicidin S; XJB-5-131; JP4-039

INTRODUCTION

Allylic Amines

Analogous to allylic alcohols, allylic amines represent useful functionalized 3-carbon building blocks for the synthesis of heterocycles and bioactive amines. In addition to oxygenations and aminations, metathesis reactions of allylic amines have been used to generate more complex derivatives (Figure 1). Several protocols are available for the synthesis of α-chiral allylic amines,[1] including the rearrangement of allylic trichloroacetimidates,[1b] Ni(0)-mediated allylic amination,[1c] C,H-bond activation, and C-C bond-forming hydrogenation.[1k] Currently, nucleophilic additions to imines represent the most versatile strategy to prepare chiral allylic amines.[1d-k] In addition to the direct addition of vinyl organometallic species,[1g-i] the reductive coupling of alkynes[1d-f] and the acylvinyl anion addition[1j] provide diastereo- and/or enantiomerically enriched products.

Jamison and coworkers developed an enantioselective synthesis of tetrasubstituted allylic amines by intermolecular coupling of a disubstituted alkyne, an imine, and triethylborane (Scheme 1).[1e] The conversion was catalyzed by a chiral [Ni(cod)$_2$]/ferrocenyl phosphane complex (**3**). A (*tert*-butyldimethylsilyloxy)ethyl group was used to enhance reactivity and selectivity in the reaction of the achiral imine (**1**), and this auxiliary group could be removed from products **4-6** via a two-step protocol without decrease in enantiomeric excess.

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The Krische group was able to form allylic amines via an asymmetric iridium-catalyzed C-C bond forming hydrogenation process related to hydroformylation reactions (Scheme 2). Hydrogenation of internal alkyne **8** in the presence of either aryl or alkyl aldimines such as **7** and chiral catalyst **9** resulted in the enantiomerically enriched trisubstituted allylic sulfonylamine **10**. The regioselectivity of the reaction with unsymmetrically substituted internal alkynes was also high.

The reaction of α-hydroxypropargylsilanes with chiral sulfinylimines to form trisubstituted allylic amines was applied by the Scheidt group (Scheme 3).[1j] Brook rearrangement of the α-hydroxypropargylsilane **13** to form the lithium allenolate was achieved with *n*-BuLi. The α-acylvinyl anion equivalent reacted with sulfinylimine (*R*)-**14** to give the β-substituted aza-Morita-Baylis-Hillman product **15** in good yield and diastereoselectivity. The (*Z*)-alkene was the preferred product in all cases.

Chiral sulfinyl imines were also utilized by Ellman and coworkers to form di-, tri- or tetrasubstituted allylic amines (Scheme 4).[1i] The sulfinyl amine (*R*)-**18** was coupled with potassium trifluoroborates **19** via Rh(I)-catalysis. Air-stable $[Rh(OH)(cod)]_2$ along with 1,2-bis-(diphenylphosphinoyl)benzene (dppbenz) gave the best yield and diastereoselectivity of the allylic sulfinylimines **20-22**.

In the development of the hydrozirconation-transmetalation-imine addition protocol for the asymmetric synthesis of (*E*)-allylic amines, our group was able to take advantage of the ease of access to functionalized alkyne starting materials. Furthermore, the carboalumination/water-accelerated imine addition chemistry allowed for the preparation of terminally disubstituted allylic amines.[2] Figure 2 provides an overview of the products available with these methodologies.

Peptide Isosteres

The use of peptides as pharmaceuticals is of considerable interest, since oligo- and polypeptides are natural ligands for receptors and enzymes. However, peptide-based orally administered drug formulations are still rare and tend to exhibit poor absorption and cell permeability as well as low bioavailability. The undesirable PK properties of peptides as well as their propensity for rapid *in vivo* degradation by peptidases have encouraged the pursuit of peptide mimetics as alternative therapeutic agents. Peptide isosteres contain a nonhydrolyzable group in place of the amide bond. In order for a rational design of these compounds to be effective, they must be able to adopt secondary structures typical for native peptides.[3] Among others, methylene amine,[4] ketomethylene,[5] hydroxyethylamine,[6] hydroxymethylene and hydroxyethylene,[7] dihydroxyethylene,[8] cyclopropylalkylamine,[9] methyl- and (trifluoromethyl)alkenes,[10] and β-amino acids[11] have been used for this purpose. Our group has studied (*E*)-alkenes[9b,10b,12] as peptide bond replacements (Figure 3),[3b,13] and the synthesis and applications of these isosteres as mitochondrial targeting compounds[14] is a major focus of our program.

Mitochondrial Targeting Agents

The cyclodecapeptide antibiotic gramicidin S displays significant resistance to peptide-cleaving proteases (Figure 4).[15] It has been shown to interact with microbial membrane lipids, and this interaction as well as its general biological profile are correlated to its secondary structure composed of an amphipathic anti-parallel β-sheet and two type II′ β-turns. Our group has studied the conformational and biological effects of isosteric substitutions with both di- and trisubstituted alkenes in the gramicidin S backbone.[13,16]

The design of the mitochondrial targeting agents XJB-5-131 and JP4-039 was inspired by the microbial membrane affinity of gramicidin S and guided by its characteristic secondary structural features. Replacement of an internal amide bond with an (*E*)-alkene moiety was envisioned to increase both the rigidity of the peptide mimetic as well as enhance its membrane permeability by removing a polar hydrogen bond donor/acceptor function. XJB-5-131, a first generation analog of gramicidin S, retained the Leu-^{D}Phe-Pro-Val-Orn segment of the parent structure to fully encompass the II′ β-turn motif.[9a] A 4-amino-TEMPO (4-AT) "pay load" was added at the *C*-terminus to serve as a scavenger of reactive oxygen species (ROS) formed in mitochondria. The structurally simplified JP4-039 possesses an alkene dipeptide isostere segment comprised of leucine and glycine residues. XJB-5-131 and JP4-039 were found to be enriched in mitochondria by factors of 600 and 30, respectively, over their cytosolic concentrations.[14c,17]

We attribute the ability of these peptide mimetics to cross cellular membranes and concentrate in mitochondria to their β-turn preference as well as their affinity for the mitochondrial lipid, cardiolipin.[14c,17] For example, the X-ray analysis of JP4-039 displays a type II′ β-turn (Figure 5). The distance in the i→i+3 intramolecular H-bond between the carbonyl of the Boc group and the nitrogen of 4-AT measures 3.30 Å. Similarly, a CD-analysis of XJB-5-131 and X-ray analyses of related biologically active peptide mimetics confirm the presence of analogous β-turns.

METHODOLOGIES AND SYNTHETIC APPLICATIONS

Imine additions

Early studies toward the synthesis of allylic amines in our group explored nucleophilic additions of vinyl zinc reagents to *N,N*-diphenylphosphinoylimines. Differentially substituted internal alkynes were synthesized by reaction of dibromoalkene **23** with butyl lithium followed by quenching with electrophiles. Methyl, trimethylsilyl, and tributylstannyl alkynes **24a-c** were then subjected to hydrozirconation[2d,18] with zirconocene hydrochloride,[19] followed by transmetalation with dimethylzinc. Addition of phosphinoylimines to the reaction mixture gave alkenes **25a-d** as a 1:1 mixture of diastereomers, which were easily separable by chromatography on SiO_2.[9b,12b] The vinyl stannane **25c** was iodinated with *N*-iodosuccinimide to provide iodoalkene **26**. These intermediates could then be reacted under various cross-coupling conditions to generate a diverse set of allylic phosphinoylamines. For example, Stille cross-coupling of vinyl stannane **25c** under microwave conditions led to the trisubstituted aryl- and heteroarylalkenes **27-29** in good yields (Scheme 6). [9b]

Vinyl iodide **26** was used to synthesize phenyl- and trifluoromethyl-substituted allylic amines **30** and **33**, respectively. Negishi cross-coupling of **26** with phenylzinc bromide provided an 86% yield of **30** (Scheme 7). Alternatively, cross-coupling could be postponed until further elaboration of the *C*- and *N*-terminal functions. The phosphinoyl and silyl groups of **26** were removed with HCl(g), and the amine was acylated with CbzCl to give carbamate **31**. Two-step oxidation of the primary alcohol to the acid followed by coupling to 2-naphthylamine provided **32**, which was converted with methyl fluorosulfonyldifluoroacetate[20] and copper thiophene carboxylate to the chromatographically separable trifluoromethyl alkenes **33a** and **33b**.

Our group also developed an accelerated carboalumination of alkynes in the presence of catalytic Cp_2ZrCl_2 and stoichiometric H_2O.[21] The intermediate vinyl alanes reacted with enantiomerically enriched sulfinyl imines to provide chiral allylic amines.[2a] For example, the vinyl alane formed from terminal alkyne **34** converted sulfinyl imine (*R*)-**35** to the trisubstituted (*E*)-alkene **36** in good yield and >95% *de* (Scheme 8). The diastereoselectivity

could be explained by a 4-membered Felkin-Anh-type transition state model.[1h,22] This methodology was extended to the synthesis of cyclopropyl alkylamines.[23] Furthermore, allylic amines could be obtained via a dimethylzinc-mediated addition of alkenyl zirconocenes to imino esters[24] and by hydrozirconation followed by transmetalation to aluminum and addition to sulfinyl imines.[2c]

PEPTIDE MIMETICS BASED ON ALLYLIC AMINES

Synthesis of a Cdc25 Inhibitor

The imine addition methodology was optimized and applied to the synthesis of new (*E*)-alkene dipeptide isosteres. Our target design was based on the crystal structure of an active site peptide inhibitor of the dual-specificity phosphatase Cdc25.[25] Monosilylation of the commercially available diol **39** followed by oxidation gave aldehyde **41** (Scheme 9). A Corey-Fuchs[26] reaction provided dibromoalkene **42** which was treated with *n*-BuLi to form alkyne **43** after quenching with MeI. Hydrozirconation[2d,18] and iodination of the internal alkyne led to the iodoalkene **44**, which could be used as a common intermediate in the formation of other trisubstituted alkene peptide isosteres.

Building block **44** was used to synthesize intermediate **50** in the synthesis of isostere **57**. Iodine-lithium exchange of **44**, followed by transmetalation to magnesium[1h] and addition to sulfinyl imine (*R*)-**45** gave **46** as a 2.5:1 mixture of diastereomers (Scheme 10). Protecting group removal, *t*-butyl carbamate formation, and oxidation of the primary alcohol led to acid **47**. Acylation of amine **48** provided the trisubstituted alkene **49**, and saponification, peptide coupling and removal of the Boc group led to the advanced intermediate **50**.

The crystal structure of tetrapeptide mimetic **49** displayed a type II′ β-turn with prototypical dihedral angles (Figure 6). Interestingly, this compound crystallized in the chiral space group P6_s1 and formed an infinite one-dimensional hydrogen-bonded chain along the z-axis. The molecules assemble in a three-fold axis around long channels, which are filled with disordered solvent molecules (Figure 7). The diameter of the channel in the rhombi measures ca. 5.5 Å, and the sides have a length of ca. 9 Å.

To complete the synthesis of **57**, phenylalanine sulfonic acid derivative **54** was prepared by reaction of commercially available aldehyde **51** with Wittig reagent **52** and tetramethylguanidine (TMG) to give alkene **53**. Stereoselective reduction of **53** and saponification provided acid **54**. This acid was then coupled to amine **50** to provide **55**. Removal of the Boc protecting group and subsequent coupling to carboxylic acid **56** gave **57**, the protected trisubstituted alkene peptide isostere analog of the known[25a] peptidic Cdc25 phosphatase inhibitor.

Synthesis of Mitochondrial Targeting Agents

Both XJB-5-131 and JP4-039 adopt type II′ β-turn structures suitable for membrane passage. Because the trisubstituted alkene **49** was also shown to adopt this β-turn, an analog of JP4-039 with a trisubstituted alkene was synthesized from iodoalkene **44** (Scheme 12). Lithium-halogen exchange of **44** followed by transmetalation with cerium(III) and addition to sulfinyl amine (*S*)-**58** provided allylic amine **59** in good yield as a 5:1 mixture of diastereomers that were separable by chromatography on SiO_2. Deprotection of **59** followed by Boc-protection of the free amine gave **60**. The primary alcohol was then oxidized to the acid and coupled to 4-AT to yield **61**.

Significantly, the hydrozirconation-transmetalation-imine addition proved to be a robust method for the scaleup of (*E*)-alkene gramicidin S analogs.[27] The synthesis of (*S*)-**65** began

with the silylation of homopropargyl alcohol **62** (Scheme 13). Hydrozirconation of this alkyne on >150 g scale with Cp_2ZrHCl,[19] transmetalation with trimethylaluminum, and addition to sulfinyl imine (*R*)-**58**[28] provided the highly diastereomerically enriched allylic sulfinyl amine (>20:1 *de* by ^1H NMR analysis of the crude reaction mixture). The commercial availability of the hydrozirconating agent Cp_2ZrHCl is limited, but the corresponding dichloride Cp_2ZrCl_2 can be obtained in bulk quantities and was converted by LAH reduction in ether to the hydrochloride. Removal of the sulfinyl group led to amine salt **64** in 96% yield. This amine was then Boc-protected and the silyl group was removed to reveal the homoallylic alcohol (*S*)-**65** in 45% overall yield. (*S*)-**65** was further used as a key intermediate to synthesize several simplified gramicidin S analogs, including XJB-5-131 and JP4-039.

Completion of the synthesis of JP4-039 from (*S*)-**65** was accomplished in just two additional steps (Scheme 14). Jones oxidation of the primary alcohol followed by coupling to 4-AT gave the mitochondrial targeting agent in 33% overall yield from commercially available **62** in 99% purity and 99% *ee*. This synthetic sequence was completed on 160 g scale.

Gratifyingly, alkene peptide isosteres such as JP4-039 can demonstrate acceptable metabolic stabilities. In C57BL/6NHsd female mice, the half-life of JP4-039 was found to be 5.0 min in the blood, 10 min in the lungs, and 60 min in the liver, heart, and intestine. A difluorinated analog **68** was designed to further increase the pharmacokinetic properties of JP4-039 (Scheme 15). The synthesis of **68** originated from the common intermediate (*S*)-**65**. Jones oxidation followed by esterification with TMS-diazomethane gave methyl ester **66**. Fluorination of **66** with *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide (NFSi) provided difluorinated ester **67**. Saponification and subsequent coupling to 4-AT led to difluoro-JP4-039 (**68**). Metabolic stabilities in pooled male mouse liver microsomes (MMLM) revealed that **68** was indeed more stable than the parent compounds, XJB-5-131 and JP4-039. Specifically, 13% and 15% of XJB-5-131 and JP4-039 were detected by LCMS after 60 min in the presence of NADPH, with 98% and 93%, respectively, remaining in the absence of NADPH. Conversely, 27% of **68** was found after 60 min in the presence of NADPH, and 91% in its absence, demonstrating a roughly 2-fold improvement in stability of the fluorinated analog in the presence of activated cytochrome P450 isoforms.

The straightforward access to (*S*)-**65** also allowed for a large-scale synthesis of XJB-5-131,[29] representing a notable improvement over the 1st generation route.[9a] XJB-5-131 was obtained in 34% overall yield in a total of 12 steps for the longest linear sequence from commercially available starting materials (Scheme 16). Specifically, Jones oxidation of (*S*)-**65**, mixed anhydride formation with pivaloyl chloride, and condensation with benzyl oxazolidinone gave imide **70**. The benzyl side chain in **71** was installed in >20:1 *dr* using an Evans asymmetric alkylation. Cleavage of the chiral auxiliary followed by coupling with tripeptide H-Pro-Val-Orn(Cbz)-OMe provided ester **72**. Saponification and coupling with 4-AT completed the synthesis. This sequence allowed for the preparation of a ca. 2 g batch of XJB-5-131 as a single detectable stereoisomer. In addition to the improved scalability of this route, its efficiency vs. the earlier process was enhanced by the enantioselective approach to allylic amine **70**, the use of a Jones oxidation for the one-step conversion of the alcohol to the acid, and the introduction of the benzyl side chain in the late-stage intermediate **70**.

PERTINENT BIOLOGICAL ASSAYS

The ability of XJB-5-131 and JP4-039 to accumulate in mitochondria,[14c,17] where they scavenge ROS and prevent hydroperoxidation of cardiolipin by cycling between nitroxide

redox states, augurs well for their application in the treatment of a number of mitochondria-related diseases as well as for radiation countermeasures (Table 1).[30,31]

Treatment with XJB-5-131 in rats subjected to lethal hemorrhagic shock prolonged survival even without resuscitation and injection with asanguinous fluids or blood.[32] Both XJB-5-131[33] and JP4-039[34] demonstrated radioprotective properties in cells and in mice. Radioprotectants could prove useful in preventing radiation damage side effects in individuals undergoing cancer radiation therapy, for example. Furthermore, JP4-039 was shown to be a mitigator[35] when it was administered to female C57Bl/6HNsd mice 24 h after the radiation event. These mice were found to have reduced peripheral blood lymphocytes, neutrophils, and bone marrow cellularity, demonstrating that JP4-039 was effective at mitigating hematopoietic syndrome.[36] These and other potential therapeutic effects of these agents are currently under further investigation in a range of *in vitro* and *in vivo* systems.

CONCLUSIONS

The mitochondrial targeting agents JP4-039 and XJB-5-131 are examples of rationally designed, functional (*E*)-alkene peptide isosteres. The preparations and evaluations of these compounds were contingent on a robust synthetic access to allylic amine building blocks. The stereoselective synthesis of these compounds and other alkene peptide isosteres is concise, high yielding, and scalable to at least a half-kg level based on the hydro(carbo)metalation-transmetalation-imine addition methodologies developed in our laboratory. Specialized organometallic reagents, such as Cp_2ZrCl_2 and trimethylaluminum can be purchased on a multi-kilogram or even multi-ton scale. As it is the case for many new methodologies, however, applications at that scale will likely require extensive further optimizations by process chemists. For example, environmental impact, heavy metal usage, toxicity, hazard and cost of organometallic reagents, cryogenics, and chromatographic purifications will have to be resolved. Nonetheless, the authors hope that new synthetic methods such as the hydro(carbo)metalation-transmetalation-imine addition will inspire the design of structurally novel drug candidates and accelerate their move into Phase I studies.

Acknowledgments

The authors thank the NSF and NIH for financial support. Drs. Corey Stephenson, Christopher Kendall, Jingbo Xiao, Jennifer Davoren, Joshua Pierce, and Marie-Céline Frantz in our laboratories at the University of Pittsburgh were valuable contributors to the synthetic work summarized in this Perspective, and Profs. Fink, Kagan, Greenberger, Epperly and Bayir, also at the University of Pittsburgh, were instrumental for the biological evaluations. We thank Dr. Steven Geib (University of Pittsburgh) for the X-ray analyses. Scale-up of the synthesis of JP4-039 was performed at Asymchem Inc.

References

1. (a) Johannsen M, Jørgensen KA. Chem Rev. 1998; 98:1689. [PubMed: 11848944] (b) Anderson CE, Overman LE. J Am Chem Soc. 2003; 125:12412. [PubMed: 14531676] (c) Berkowitz DB, Maiti G. Org Lett. 2004; 6:2661. [PubMed: 15281738] (d) Grossman RB, Davis WM, Buchwald SL. J Am Chem Soc. 1991; 113:2321.(e) Patel SJ, Jamison TF. Angew Chem Int Ed. 2004; 43:3941.(f) Ngai M-Y, Barchuk A, Krische MJ. J Am Chem Soc. 2007; 129:12644. [PubMed: 17914825] (g) Denmark SE, Weber T, Piotrowski DW. J Am Chem Soc. 1987; 109:2224.(h) Cogan DA, Liu G, Ellman J. Tetrahedron. 1999; 55:8883.(i) Brak K, Ellman JA. J Am Chem Soc. 2009; 131:3850. [PubMed: 19256498] (j) Reynolds TE, Binkley MS, Scheidt KA. Org Lett. 2008; 10:5227. [PubMed: 18959427] (k) Skucas E, Ngai M-Y, Komanduri V, Krische MJ. Acct Chem Res. 2007; 40:1394.
2. (a) Wipf P, Nunes RL, Ribe S. Helv Chim Acta. 2002; 85:3478.(b) Wipf P, Kendall C, Stephenson CRJ. J Am Chem Soc. 2003; 125:761. [PubMed: 12526676] (c) Wipf P, Pierce JG. Org Lett. 2006; 8:3375. [PubMed: 16836409] (d) Wipf P, Kendall C. Top Organomet Chem. 2004; 8:1.

3. (a) Vagner J, Qu H, Hruby VJ. Curr Opin Chem Biol. 2008; 12:292. [PubMed: 18423417] (b) Wipf P, Xiao J, Stephenson CRJ. Chimia. 2009; 63:764. [PubMed: 20725595]
4. (a) Li CS, Deschenes D, Desmarais S, Falgueyret J-P, Gauthier JY, Kimmel DB, Léger S, Massé F, McGrath ME, McKay DJ, Percival MD, Riendeau D, Rodan SB, Thérien M, Truong V-L, Wesolowski G, Zamboni R, Black WC. Bioorg Med Chem Lett. 2006; 16:1985. [PubMed: 16413777] (b) Zanda M. New J Chem. 2004; 28:1401.(c) Leftheris K, Kline T, Vite GD, Cho YH, Bhide RS, Patel DV, Patel MM, Schmidt RJ, Weller HN, Andahazy ML, Carboni JM, Gullo-Brown JL, Lee FYF, Ricca C, Rose WC, Yan N, Barbacid M, Hunt JT, Meyers CA, Seizinger BR, Zahler R, Manne V. J Med Chem. 1996; 39:224. [PubMed: 8568812]
5. (a) Dondoni A, Perrone D. Tetrahedron Lett. 1992; 33:7259.(b) Vabeno J, Lejon T, Nielsen CU, Steffansen B, Chen W, Ouyang H, Borchardt RT, Luthman K. J Med Chem. 2004; 47:1060. [PubMed: 14761208]
6. Reid RC, Pattenden LK, Tyndall JDA, Martin JL, Walsh T, Fairlie DP. J Med Chem. 2004; 47:1641. [PubMed: 15027855]
7. (a) Myers AG, Barbay JK, Zhong B. J Am Chem Soc. 2001; 123:7207. [PubMed: 11472148] (b) Aoyagi Y, Williams RM. Tetrahedron. 1998; 54:10419.(c) Lama T, Del Valle SE, Genest N, Lubell WD. Int J Pept Res Ther. 2007; 13:355.
8. Righi G, Ronconi S, Bonini C. Eur J Org Chem. 2002; 2002:1573.
9. (a) Wipf P, Xiao J, Jiang J, Belikova NA, Tyurin VA, Fink MP, Kagan VE. J Am Chem Soc. 2005; 127:12460. [PubMed: 16144372] (b) Wipf P, Xiao J, Geib SJ. Adv Synth Catal. 2005; 347:1605.
10. (a) Jakobsche CE, Peris G, Miller SJ. Angew Chem Int Ed. 2008; 47:6707.(b) Wipf P, Henninger TC, Geib SJ. J Org Chem. 1998; 63:6088. [PubMed: 11672228]
11. (a) Price JL, Horne WS, Gellman SH. J Am Chem Soc. 2010; 132:12378. [PubMed: 20718422] (b) Seebach D, Lukaszuk A, Patora-Komisarska K, Podwysocka D, Gardiner J, Ebert M-O, Reubi JC, Cescato R, Waser B, Gmeiner P, Hübner H, Rougeot C. Chem Biodivers. 2011; 8:711. [PubMed: 21560227]
12. (a) Daly MJ, Ward RA, Thompson DF, Procter G. Tetrahedron Lett. 1995; 36:7545.(b) Wipf P, Xiao J. Org Lett. 2005; 7:103. [PubMed: 15624988] (c) Jenkins CL, Vasbinder MM, Miller SJ, Raines RT. Org Lett. 2005; 7:2619. [PubMed: 15957905] (d) Fu Y, Bieschke J, Kelly JW. J Am Chem Soc. 2005; 127:15366. [PubMed: 16262389] (e) Tomita K, Narumi T, Niida A, Oishi S, Ohno H, Fujii N. Pept Sci. 2007; 88:272.(f) Wiktelius D, Luthman K. Org Biomol Chem. 2007; 5:603. [PubMed: 17285166] (g) Bandur NG, Harms K, Koert U. Synthesis. 2007; 2007:2720.(h) Wipf P, Fritch PC. J Org Chem. 1994; 59:4875.(i) Wipf P, Henninger TC. J Org Chem. 1997; 62:1586.
13. Xiao J, Weisblum B, Wipf P. J Am Chem Soc. 2005; 127:5742. [PubMed: 15839644]
14. (a) Fink MP, Macias CA, Xiao J, Tyurina YY, Jiang J, Belikova N, Delude RL, Greenberger JS, Kagan VE, Wipf P. Biochem Pharmacol. 2007; 74:801. [PubMed: 17601494] (b) Kanai A, Zabbarova I, Amoscato A, Epperly M, Xiao J, Wipf P. Org Biomol Chem. 2007; 5:307. [PubMed: 17205174] (c) Jiang J, Kurnikov I, Belikova NA, Xiao J, Zhao Q, Amoscato AA, Braslau R, Studer A, Fink MP, Greenberger JS, Wipf P, Kagan VE. J Pharmacol Exp Ther. 2007; 320:1050. [PubMed: 17179468]
15. Lee DL, Hodges RS. Pept Sci. 2003; 71:28.
16. Xiao J, Weisblum B, Wipf P. Org Lett. 2006; 8:4731. [PubMed: 17020289]
17. Kagan VE, Wipf P, Stoyanovsky D, Greenberger JS, Borisenko G, Belikova NA, Yanamala N, Samhan Arias AK, Tungekar MA, Jiang J, Tyurina YY, Ji J, Klein-Seetharaman J, Pitt BR, Shvedova AA, Bayir H. Adv Drug Delivery Rev. 2009; 61:1375.
18. Wipf P, Jahn H. Tetrahedron. 1996; 52:12853.
19. (a) Hart DW, Schwartz J. J Am Chem Soc. 1974; 96:8115.(b) Schwartz J, Labinger JA. Angew Chem Int Ed. 1976; 15:333.
20. (a) Chen Q-Y, Wu S-W. J Chem Soc Chem Commun. 1989:705.(b) Fei X-S, Tian W-S, Chen Q-Y. J Chem Soc Perkin Trans. 1998; 1:1139.
21. Wipf P, Lim S. Angew Chem Int Ed. 1993; 32:1068.

22. (a) Shaw AW, deSolms SJ. Tetrahedron Lett. 2001; 42:7173.(b) Fujisawa T, Kooriyama Y, Shimizu M. Tetrahedron Lett. 1996; 37:3881.(c) Plobeck N, Powell D. Tetrahedron: Asymmetry. 2002; 13:303.
23. (a) Wipf P, Kendall C, Stephenson CRJ. J Am Chem Soc. 2001; 123:5122. [PubMed: 11457353] (b) Wipf P, Kendall C, Stephenson CRJ. J Am Chem Soc. 2002; 125:761. [PubMed: 12526676] (c) Wipf P, Kendall C. Chem Eur J. 2002; 8:1778. [PubMed: 11933105]
24. Wipf P, Stephenson CRJ. Org Lett. 2003; 5:2449. [PubMed: 12841752]
25. (a) Baeurle S, Blume T, Guenther J, Henschel D, Hillig RC, Husemann M, Mengel A, Parchmann C, Schmid E, Skuballa W. Bioorg Med Chem Lett. 2004; 14:1673. [PubMed: 15026048] (b) Lazo JS, Aslan DC, Southwick EC, Cooley KA, Ducruet AP, Joo B, Vogt A, Wipf P. J Med Chem. 2001; 44:4042. [PubMed: 11708908] (c) Brezak M-C, Quaranta M, Contour-Galcera M-O, Lavergne O, Mondesert O, Auvray PØ, Kasprzyk PG, Prevost GP, Ducommun B. Mol Cancer Ther. 2005; 4:1378. [PubMed: 16170030]
26. Corey EJ, Fuchs PL. Tetrahedron Lett. 1972; 13:3769.
27. Frantz M-C, Pierce JG, Pierce JM, Kangying L, Qingwei W, Johnson M, Wipf P. Org Lett. 2011; 13:2318. [PubMed: 21452836]
28. Staas DD, Savage KL, Homnick CF, Tsou NN, Ball RG. J Org Chem. 2002; 67:8276. [PubMed: 12423170]
29. Frantz M-C, Skoda EM, Davoren JE, Wang Z, Epperly MW, Stripay JL, Tyurin VA, Fink B, Greenberger JS, Bayir H, Rob-bins P, Niedernhofer L, Kagan VE, Wipf P. Manuscript in Preparation. 2011
30. Hoye AT, Davoren JE, Wipf P, Fink MP, Kagan VE. Acc Chem Res. 2008; 41:87. [PubMed: 18193822]
31. Frantz M-C, Wipf P. Environ Mol Mutagen. 2010; 51:462. [PubMed: 20175113]
32. Macias CA, Chiao JW, Xiao J, Arora Devinder S, Tyurina YY, Delude RL, Wipf P, Kagan VE, Fink MP. Annals of Surg. 2007; 245:305.
33. (a) Jiang J, Belikova Natalia A, Hoye Adam T, Zhao Q, Epperly Michael W, Greenberger Joel S, Wipf P, Kagan Valerian E. Int J Radiat Oncol Biol Phys. 2008; 70:816. [PubMed: 18262096] (b) Rwigema J-CM, Beck B, Wang W, Doemling A, Epperly MW, Shields D, Goff Julie P, Franicola D, Dixon T, Frantz M-C, Wipf P, Tyurina Y, Kagan VE, Wang H, Greenberger JS. Int J Radiat Oncol Biol Phys. 2011; 80:860. [PubMed: 21493014]
34. (a) Epperly MW, Goff JP, Li S, Gao X, Wipf P, Dixon T, Wang H, Franicola D, Shen H, Rwigema J-CM, Kagan VE, Bernard M, Greenberger JS. In Vivo. 2010; 24:811. [PubMed: 21164038] (b) Gokhale A, Rwigema J-C, Epperly MW, Glowacki J, Wang H, Wipf P, Goff JP, Dixon T, Patrene K, Greenberger JS. In Vivo. 2010; 24:377. [PubMed: 20668303]
35. Rajagopalan MS, Gupta K, Epperly MW, Franicola D, Zhang X, Wang H, Zhao H, Tyurin VA, Pierce JG, Kagan VE, Wipf P, Kanai AJ, Greenberger JS. In Vivo. 2009; 23:717. [PubMed: 19779106]
36. Goff JP, Epperly MW, Dixon T, Wang H, Franicola D, Shields D, Wipf P, Li S, Gao X, Greenberger JS. In Vivo. 2011; 25:315. [PubMed: 21576404]
37. Tyurina YY, Tyurin VA, Kaynar AM, Kapralova VI, Wasserloos K, Li J, Mosher M, Wright L, Wipf P, Watkins S, Pitt BR, Kagan VE. Am J Physiol. 2010; 299:L73.
38. Ji J, Kline A, Cheng J, Wipf P, Tyurin VA, Alexander H, Kochanek PM, Kagan VE, Bayir HJ. J Neurotrauma. 2009; 26:A3.

ABBREVIATIONS

4-AT	4-amino TEMPO
BARF	$[B[3,5\text{-}(CF_3)_2C_6H_3]_4]$
Cbz	carboxybenzyl
cod	cyclooctadiene

DEPBT	3-(diethylphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one
DMAP	4-dimethylaminopyridine
DIPEA	*N,N*-diisopropylethylamine
dppbenz	1,2-bis(diphenylphosphino)benzene
EDCI	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
HOBt	hydroxybenzotriazole
NFSi	*N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide
NMO	*N*-methylmorpholine *N*-oxide
PCC	pyridinium chlorochromate
PyBop	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
ROS	reactive oxygen species
TBS	*tert*-butyldimethylsilyl
TMG	tetramethylguanidine

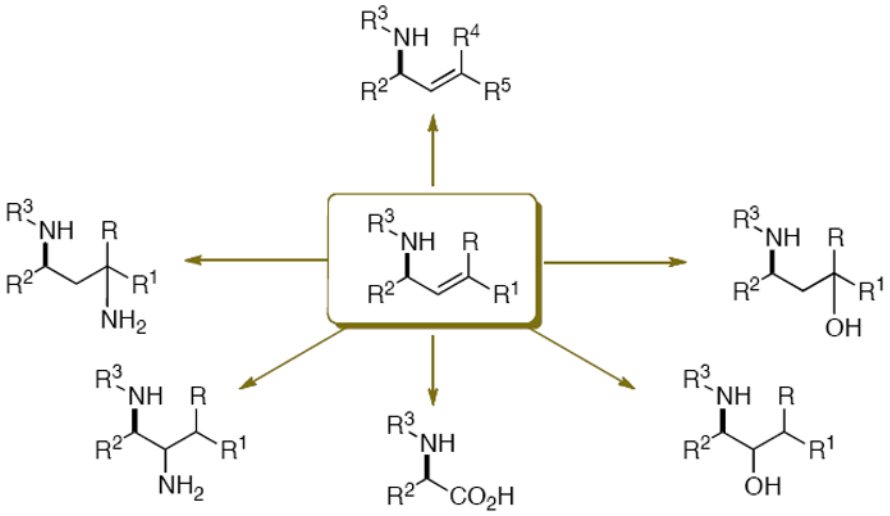


Figure 1.
Representative synthetic transformations of allylic amine building blocks.

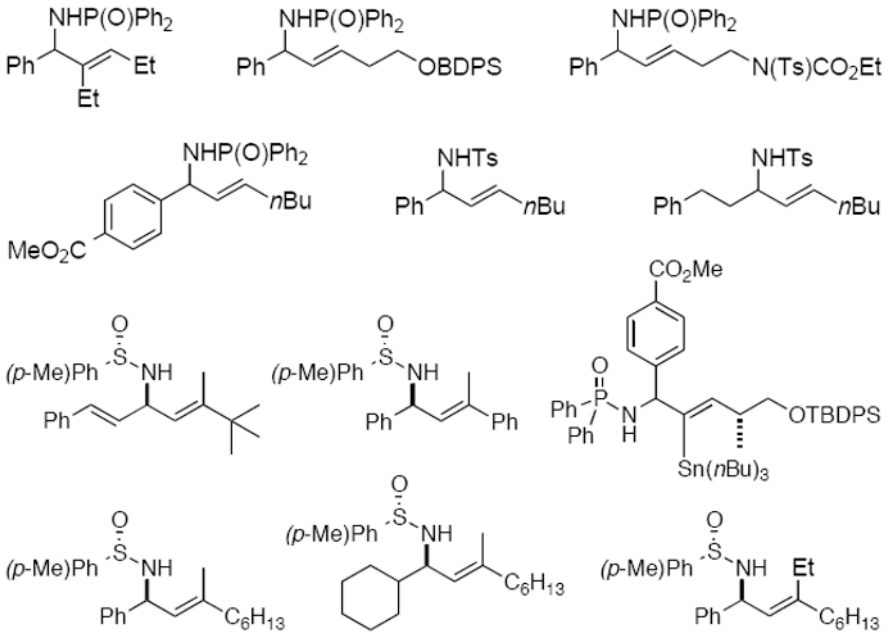


Figure 2.
Representative allylic amine building blocks obtained with alkyne hydro(carbo)metalation-imine addition methods.

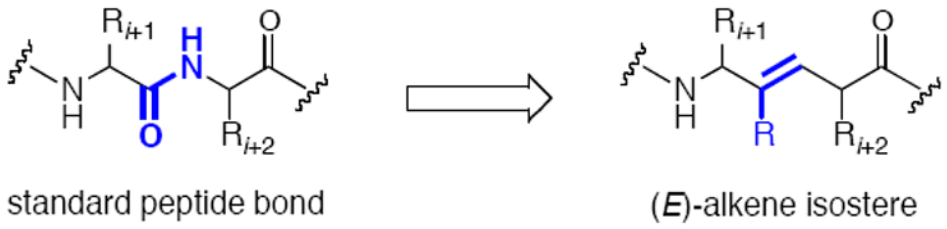


Figure 3.
Structure of (*E*)-alkene peptide isosteres as peptide bond replacements.

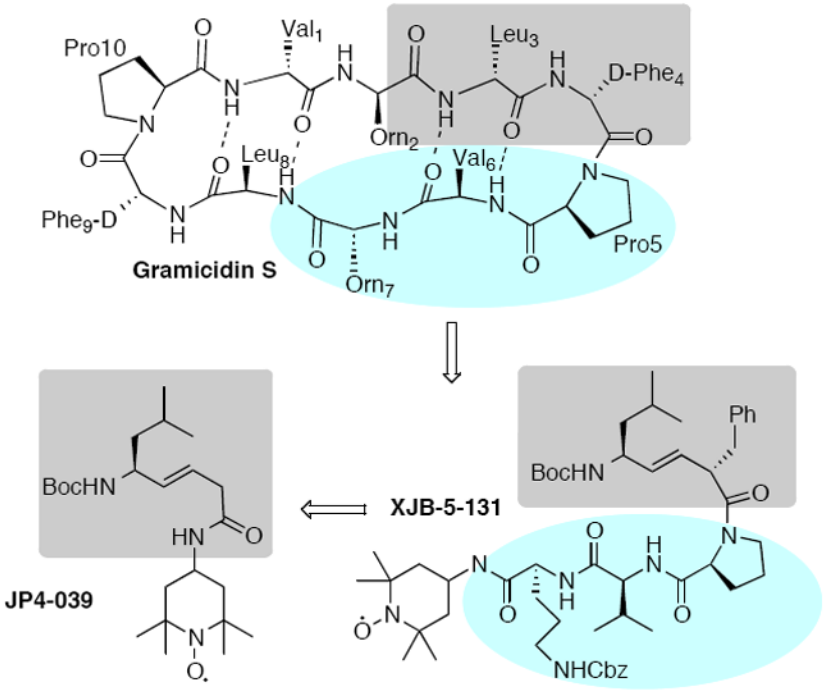


Figure 4.
Mitochondrial targeting agents based on the antibiotic gramicidin S.

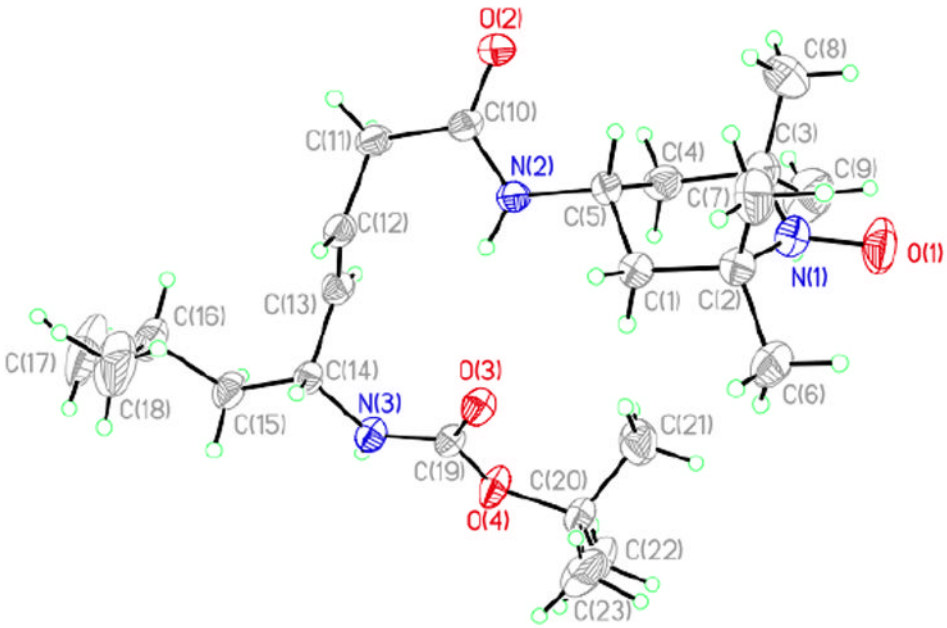


Figure 5.
The crystal structure of JP4-039 reveals a type II′ β-turn.

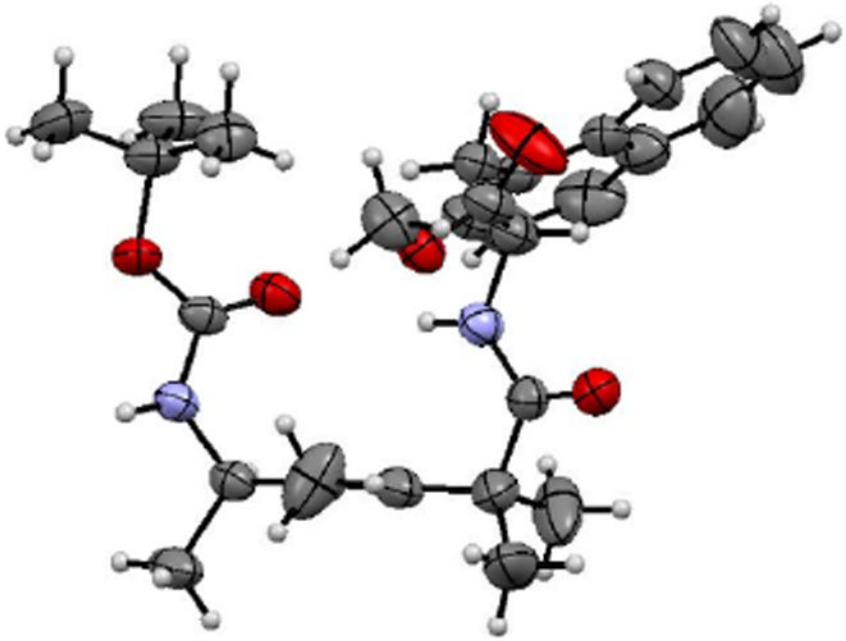


Figure 6.
Crystal structure of **49**.

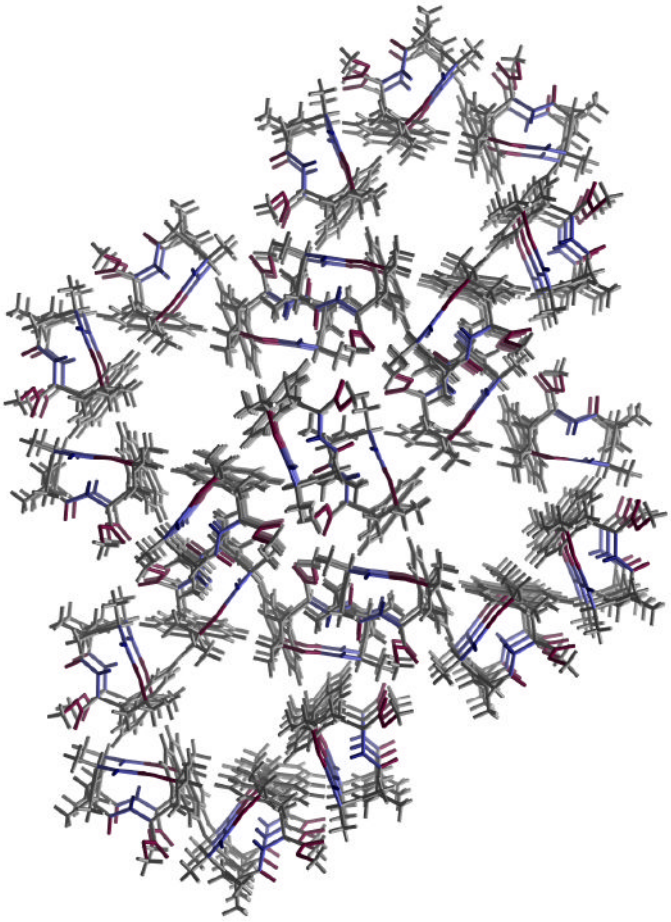
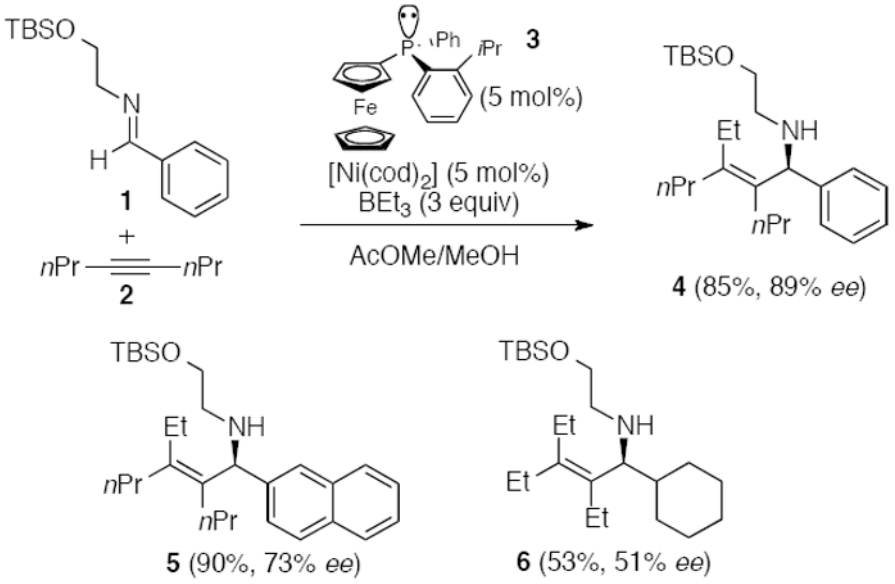
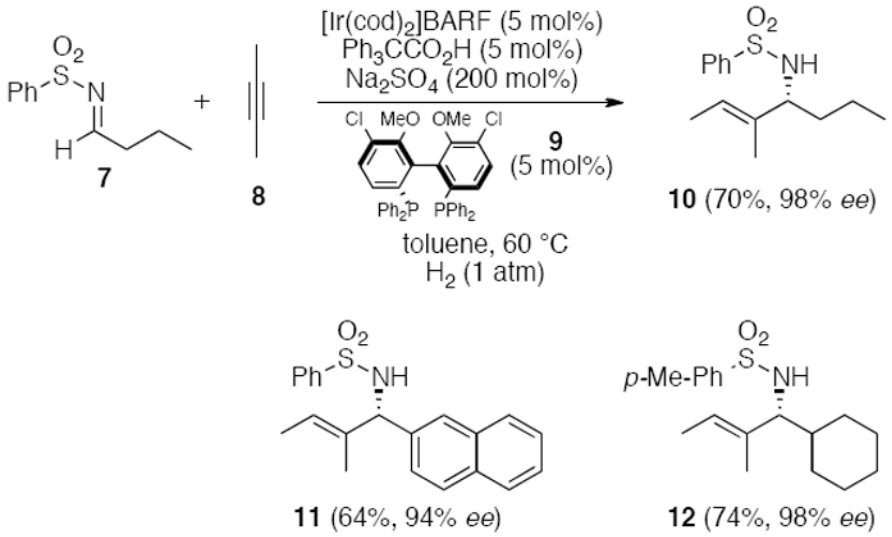


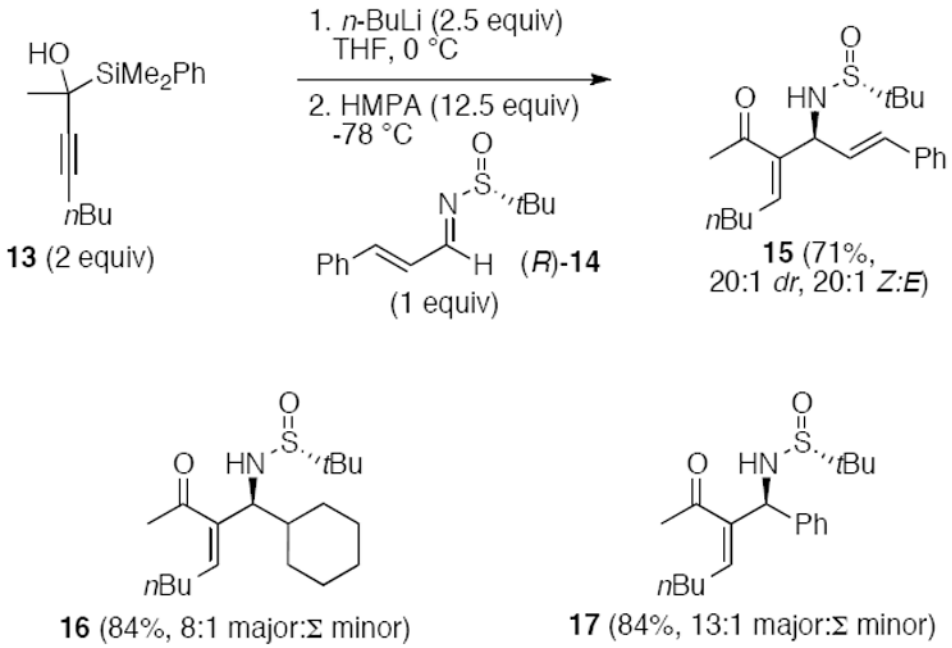
Figure 7.
Crystal structure of **49** showing four solvent channels.



Scheme 1.
Ni-catalyzed intermolecular coupling to prepare enantiomerically enriched allylic amines.[1e]

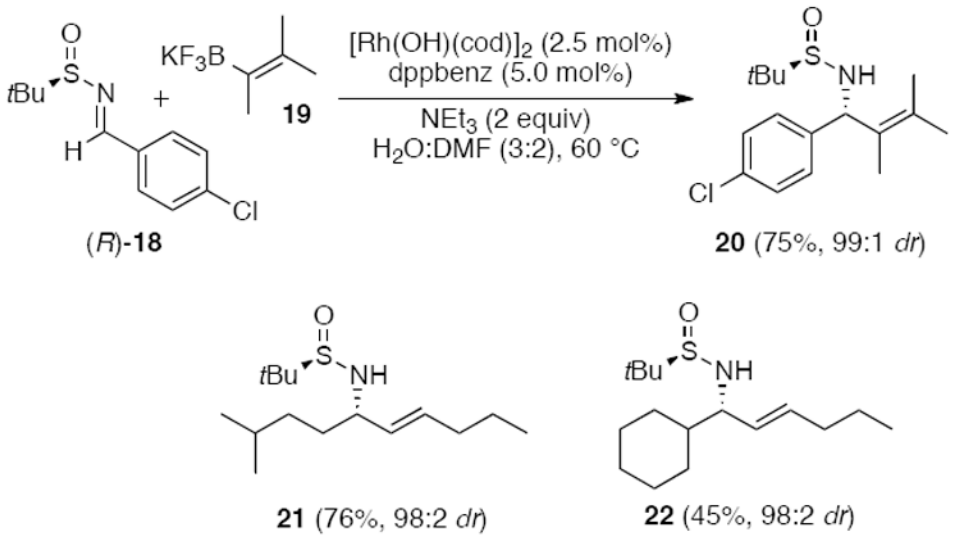


Scheme 2.
Reductive coupling of alkynes with *N*-arylsulfonyl imines.[1f]

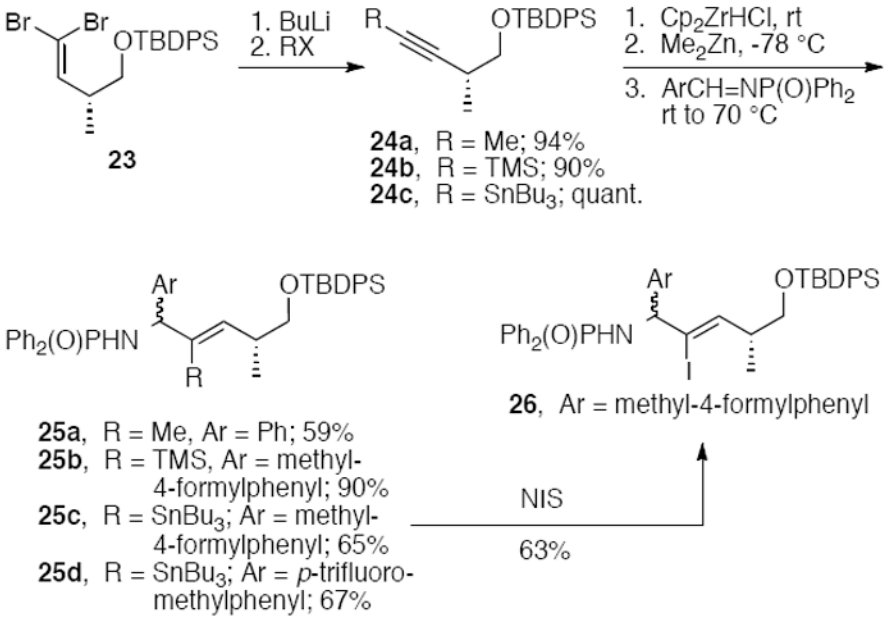


Scheme 3.

α-Acylvinyl anion addition to imines (major:Σminor refers to the ratio of the major product as drawn to the sum of all minor products).[1j]

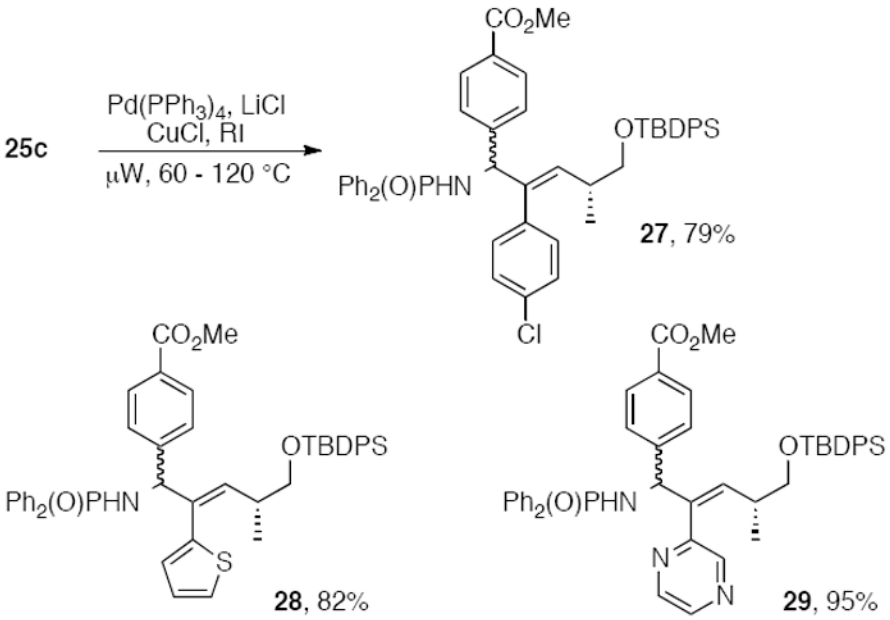


Scheme 4.
Rh(I)-catalyzed addition of alkenyl trifluoroborates to *N-tert*-butylsulfinylimines.[1i]

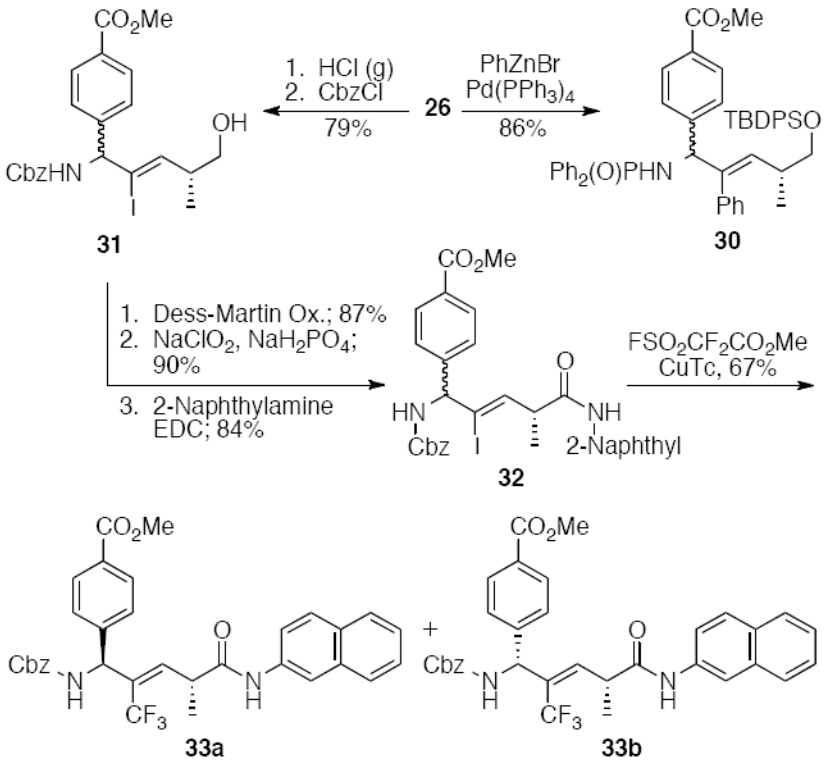


Scheme 5.

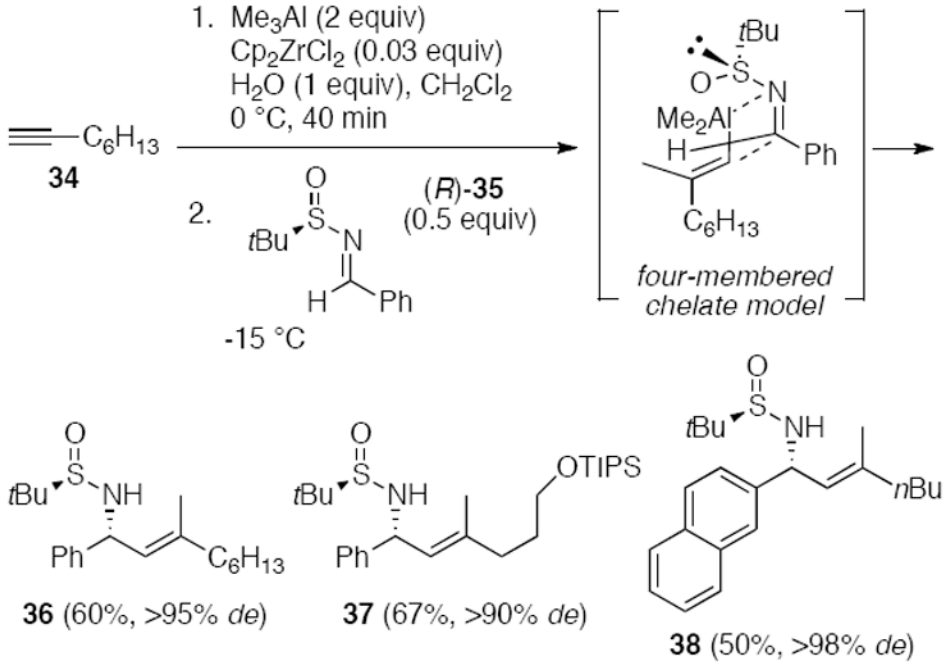
Hydrozirconation/transmetalation/imine addition approach to trisubstituted allylic amines.[9b,12b]



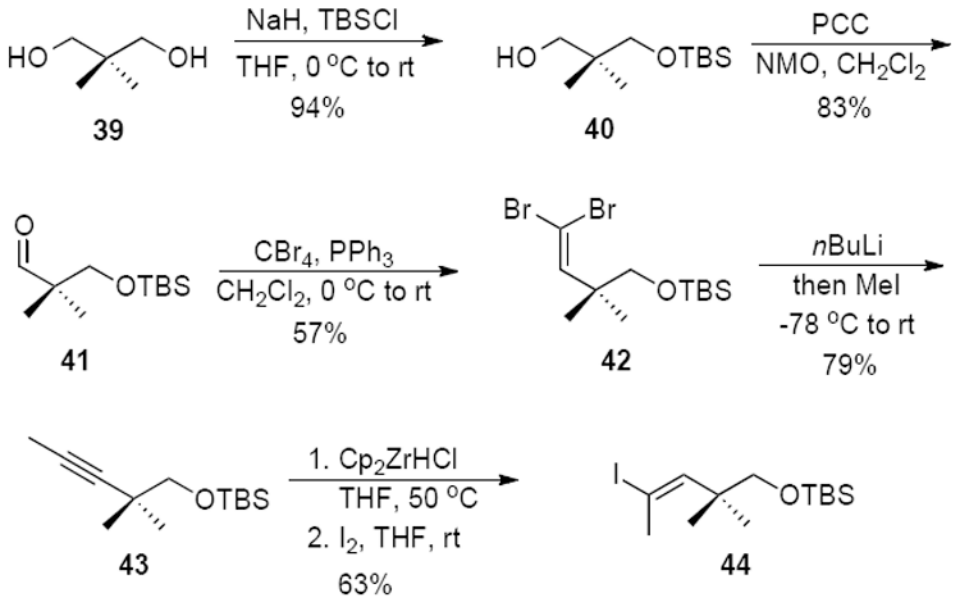
Scheme 6.
Microwave-accelerated Stille crosscouplings of **25c**.[9b]



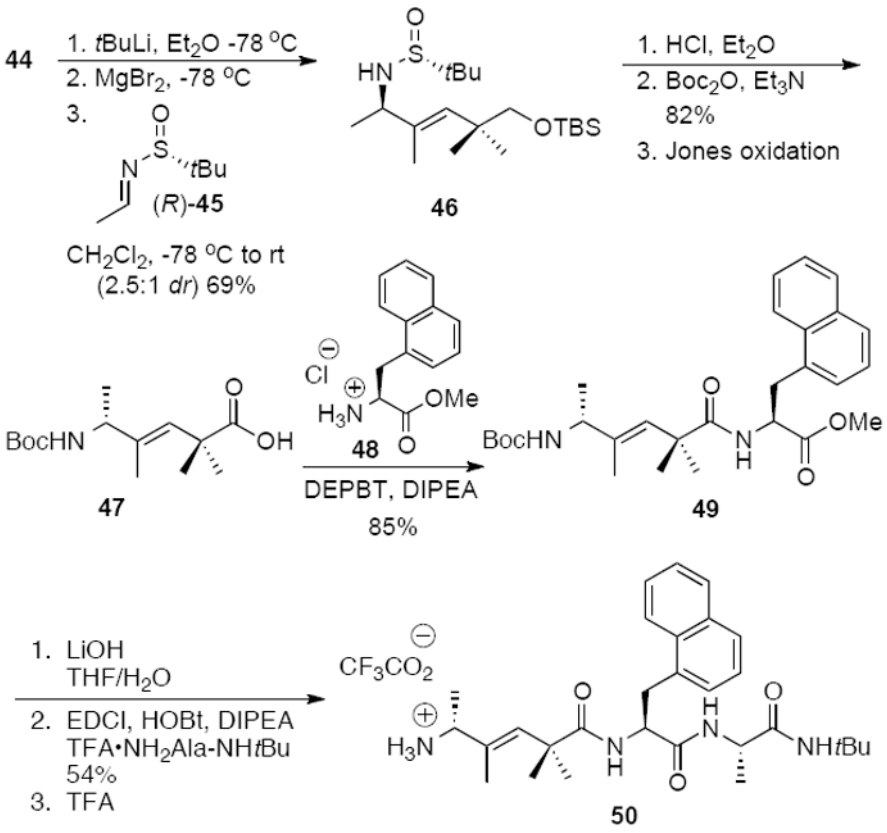
Scheme 7.
Pd-catalyzed arylation of iodoalkene **26** and trifluoromethylation of iodoalkene **32**.[9b]



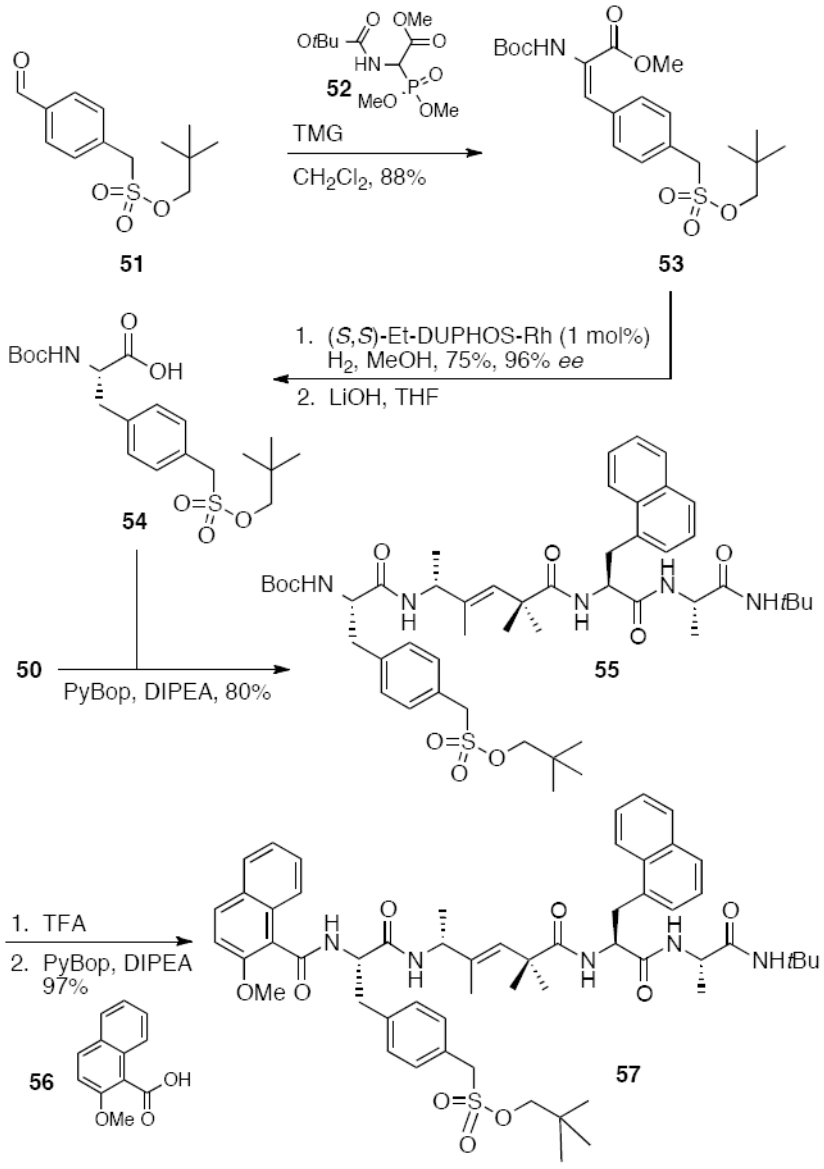
Scheme 8.
Alkyne carboalumination/sulfinyl imine addition as a stereoselective entry to (*E*)-allylic amines.[2a]



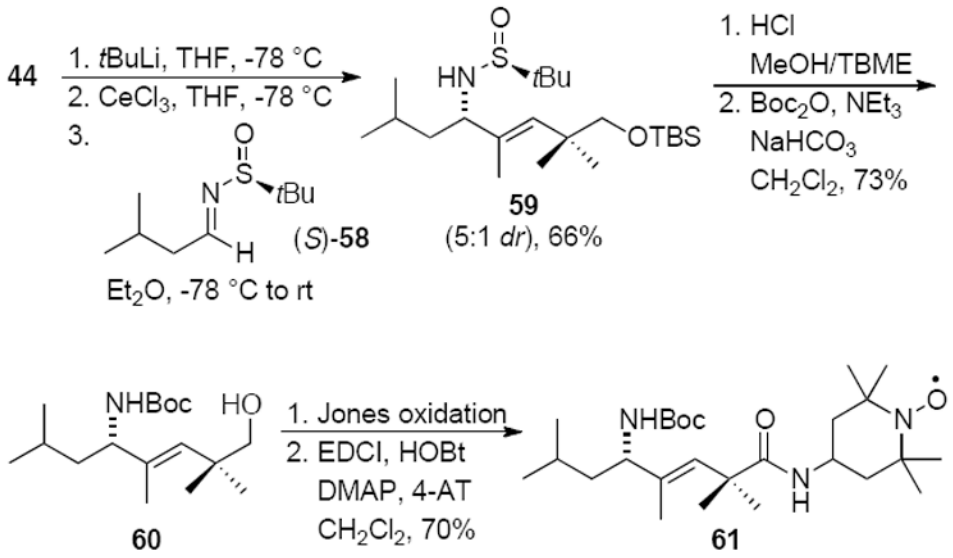
Scheme 9.
Synthesis of (*E*)-iodoalkene **44** by hydrozirconation of internal alkyne **43**.



Scheme 10.
Synthesis of allylic amine **50**.

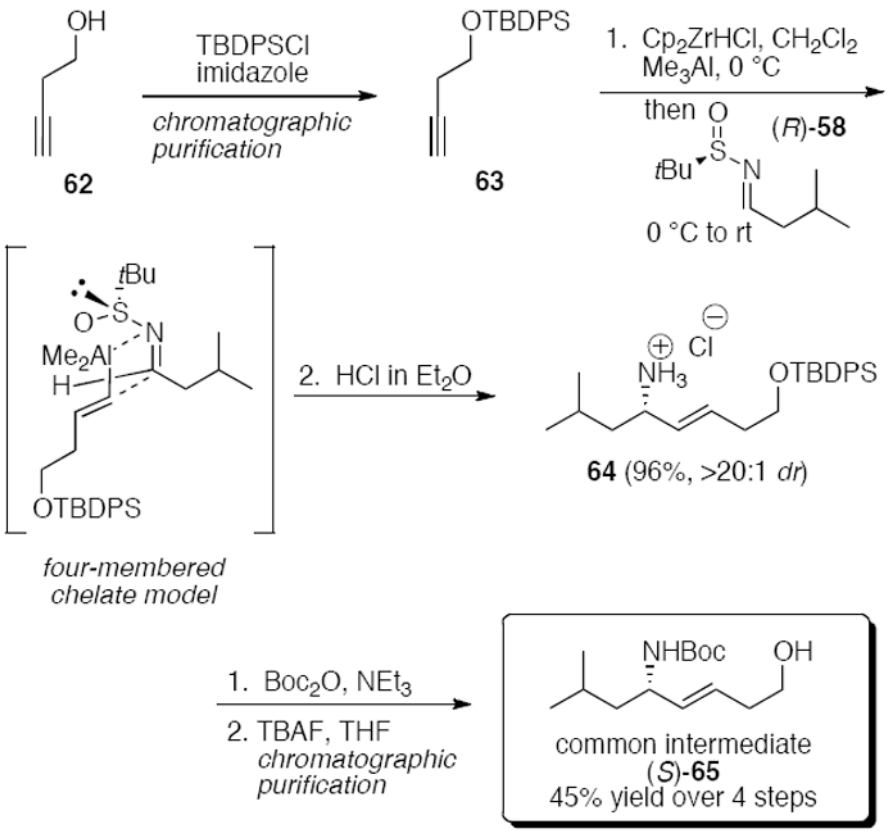


Scheme 11.
Completion of the synthesis of the protected alkene peptide isostere **57**.

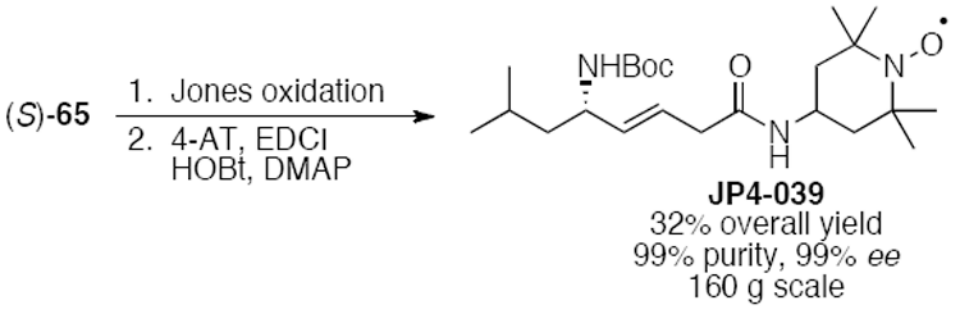


Scheme 12.

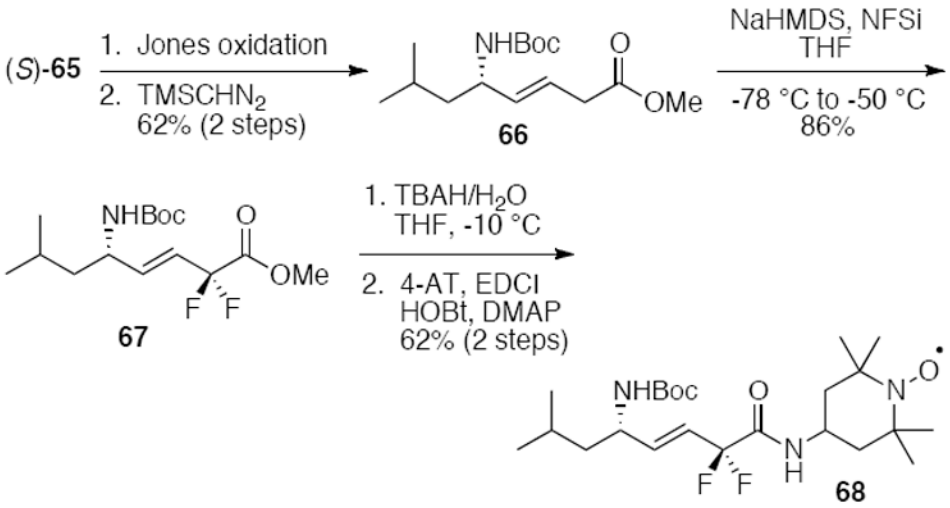
Synthesis of trisubstituted (*E*)-alkene peptide isostere **61** designed for mitochondrial targeting and scavenging of ROS.



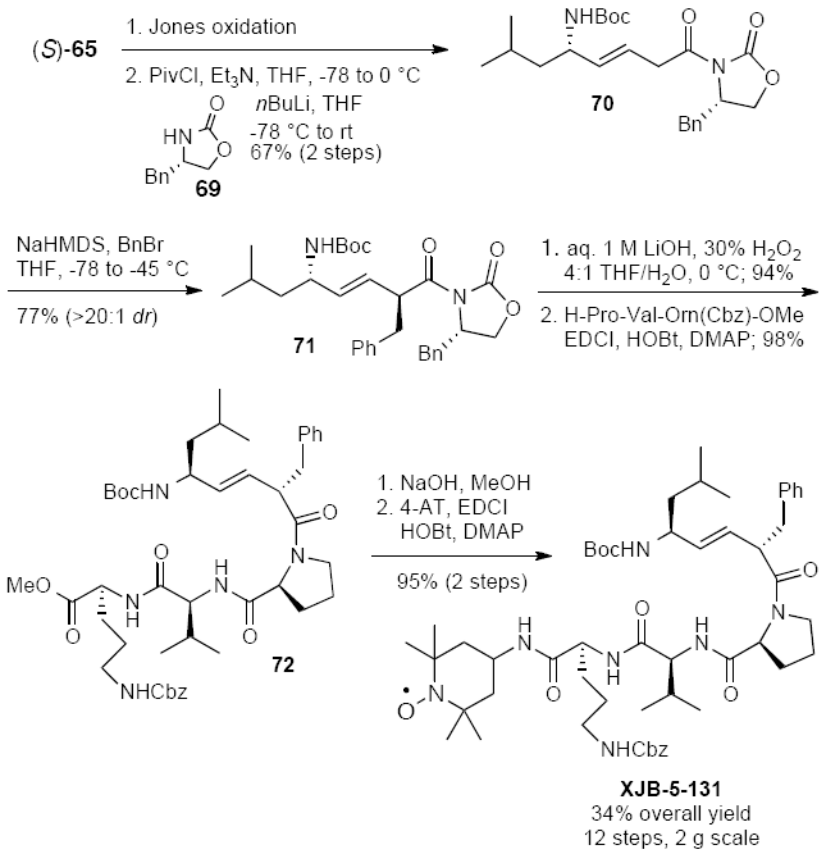
Scheme 13.
Large-scale synthesis of allylic amine intermediate (*S*)-**65**.[27]



Scheme 14.
Completion of the enantioselective synthesis of JP4-039 from carbamate (*S*)-**65**.[27]



Scheme 15.
Stereoselective synthesis of the difluorinated analog **68** from (*S*)-**65**.[27]



Scheme 16.
2nd Generation synthesis of XJB-5-131 from (*S*)-**65**.[29]

Table 1

Overview of ongoing biological studies with XJB-5-131 and JP4-039.

Biological Test	Results with XJB-5-131	Results with JP4-039
Lethal hemorrhagic shock	Significant prolonged survival in rats[32]	n.d.
Radiation protection	n.d.	Accelerated bone wound healing in irradiated mice;[34b] increased survival in mice with esophagitis[34a]
Radiation mitigation	n.d.	Accelerated bone wound healing in irradiated mice;[34b] reduction in damage to irradiated 32Dcl cells at 24 h[35]
Hyperoxic acute lung injury	Prevents CL oxidation; decreased apoptosis in concentration-dependent manner[37]	n.d.
Acute brain injury	Reduced neuronal death in vitro and in vivo; reduced behavioral deficits in rats[38]	n.d.

MPEC: mouse pulmonary endothelial cell; CL: cardiolipin; n.d.: not determined.