Published in final edited form as:
J Org Chem. 2010 December 3; 75(23): 8048–8059. doi:10.1021/jo101535d.

Preparation of Stereodefined Homoallylic Amines from the Reductive Cross-Coupling of Allylic Alcohols with Imines

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Abstract

Regio-, diastereo-, and enantioselective coupling reactions between imines and allylic alcohols have been developed. These coupling reactions deliver complex homoallylic amine products through a convergent C–C bond forming process that does not proceed through intermediate allylic organometallic reagents. In general, convergent coupling, by exposure of an allylic alkoxide to a preformed Ti–imine complex, occurs with allylic transposition in a predictable and stereocontrolled manner. While simple diastereoselection in these reactions is high, delivering *anti*-products with ≥ 20:1 selectivity, the organometallic transformation described is compatible with a diverse range of functionality and substrates (including: aliphatic and aromatic imines, allylic silanes, trisubstituted alkenes, vinyl- and aryl halides, trifluoromethyl groups, thioethers, and aromatic heterocycles). Alkene geometry of the products is a complex function of the allylic alcohol structure, and is consistent with a mechanistic proposal based on *syn*-carbometalation followed by *syn*-elimination by way of a boat-like transition state geometry. Single asymmetric coupling reactions provide a means to translate the stereochemical information of the allylic alcohol to the homoallylic amine with very high levels of fidelity, or to control diastereoselection in the coupling reactions of achiral allylic alcohols with chiral imines. Double asymmetric coupling reactions are also described that afford a unique means to control stereoselection in these complex convergent coupling processes. Finally, empirical models are proposed that are consistent with the observed stereochemical course of these coupling reactions en route to chiral homoallylic amines possessing di- or trisubstituted alkenes, and *anti*- or *syn*- relative stereochemistry at the allylic and homoallylic positions. Overall, the bond construction enabled by this Ti-mediated reductive cross-coupling is unmatched by available methods in organic chemistry.

Introduction

Methods that accomplish bimolecular (convergent) C–C bond formation define the backbone of organic synthesis.[1] Despite their central role in the construction of natural products and synthetic small molecules of biological significance, the broad classes of reactions suitable for complex convergent C–C bond formation remain rather limited and include reactions based on: 1) nucleophilic substitution, 2) nucleophilic addition to polarized π-bonds, 3) cycloaddition, 4) metal-catalyzed “cross-coupling”, and 5) crossed olefin metathesis. Arguably, carbonyl addition chemistry is among the most powerful subclass of convergent coupling, offering opportunities for fragment union through the generation of a

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diverse range of stereodefined architecture (including di- and tri-substituted alkenes, β-hydroxy carbonyls, allylic- and homoallylic alcohols).[2]

Carbonyl allylation is a subset of carbonyl addition chemistry that, over the last thirty years, has emerged as a particularly attractive method for acyclic stereocontrol, offering highly stereoselective pathways to homoallylic alcohols and amines.[3] The vast majority of established methods for carbonyl allylation, while powerful, depend on the use of allylic organometallic reagents. Despite the discovery of catalytic methods for the *in situ* generation of such reagents, the dependence on accessing an allylic organometallic species has generally limited the utility of such processes to the addition of simple unsaturated hydrocarbon fragments.[4, 5] While the synthesis and application of more functionalized allylic organometallic reagents for complex fragment union is possible, as illustrated in Figure 1 such processes are often complicated by: 1) Functional group tolerance in the preparation of the allylic organometallic reagent (**A** → **B**^{1}/**B**^{2}), 2) challenges associated with the control of site-selectivity in the metalation step (**A** → **B**^{1}/**B**^{2}), 3) difficulties in controlling the regioselectivity of C–C bond formation [due to (a) the propensity for allylic isomerization of the intermediate allylorganometallic (**B**^{1} ⇌ **B**^{2}), and (b) competition between α- vs γ- attack], and 4) problems associated with stereoselection [both tetrahedral stereochemistry and olefin geometry (i.e. **C** vs **E**, or **D** vs **F**)]. In cases where the allylic metal reagent is generated in a catalytic fashion, functional group tolerance is often enhanced, but complexities still remain due to competing isomerization of the allylic metal species, and the aforementioned issues with regio- and stereoselection in the C–C bond forming event.[5] As such, the impact that carbonyl allylation has in complex convergent bond construction, independent of whether such processes are rendered catalytic in the metal, remains fundamentally limited.

An orthogonal strategy for allyltransfer can be envisioned to proceed in an umpolung sense,[6] with bond formation occurring between a carbonyl-derived anion and an allylic electrophile (Figure 2A). In the simplest of analyses, such a transformation has related challenges to the use of allylic organometallic reagents, where issues of regioselection derive instead from a competition between S_N2 and S_N2' modes of addition, leading to the isomeric products of formal allyl-transfer (**3** and **4**). While the regiochemical course of transformations in this class have the potential to be influenced by the character of the groups flanking the allyl-unit (R^3 and R^4), and the nature of the metal counterion associated with **1**, major barriers associated with the control of relative and absolute stereochemistry combine to further complicate this subset of potential coupling processes.[7]

As depicted in Figure 2B, a related reaction with a heteroatom-substituted metallacyclopropane **5** was reasoned to proceed through a mechanistically distinct process, where bimolecular C–C bond formation would result from carbometalation of **2** (via a formal metal-centered [2+2+1] process) in preference to simple nucleophilic addition (via S_N2 or S_N2' reaction pathways). The resulting isomeric metallacyclopropanes **6** and **7** would differ with respect to stability and reactivity, affording a pathway to **3** by elimination of **6**. Control of this process could derive from one of two basic mechanistic considerations. If the carbometalation process (**5** + **2** → **6** or **7**) is reversible, the elimination reaction (**6** → **3**) may represent a means to funnel the mixture of metallacycles (**6** + **7**) to the desired product **3**, through a process that would have the potential to offer stereochemical control via selective elimination through the lowest energy transition state. Alternatively, if the carbometalation process were to proceed under kinetic control, then the stereochemical information derived from the carbometalation (en route to metallacyclopentane **6**) would translate directly to the relative stereochemistry of the product, assuming that the elimination reaction would proceed in a mechanistically predictable fashion (*syn*- or *anti*-). While glimpses of this mode of reactivity with Cp_2Zr–imine complexes were reported twenty years ago,[8] the complex

issues associated with selectivity that are critical to the development of a broadly useful convergent coupling reaction remain ill-defined.[9]

Here, we present a full account of the scope and limitations of a mild and general titanium alkoxide-mediated coupling reaction between allylic alcohols and imines as a route to stereochemically defined and highly functionalized homoallylic amines (Figure 3A).[10] The scope of these reactions now encompasses: 1) the coupling of aromatic and aliphatic imines, 2) enantioselective allyltransfer through the use of chiral allylic alcohols, 3) double asymmetric coupling as a strategy to override inherent trends in selectivity of single asymmetric reactions, 4) the use of coupling partners bearing a diverse range of functionality (including di- and trisubstituted alkenes, thioethers, allylic silanes, aromatic heterocycles, and aliphatic, vinyl- and aromatic halides), and 5) stereodivergent coupling reactions to afford a range of substituted homoallylic amines (Figure 3B).

Background Associated with Ti-alkoxides in Azametallacyclopropane-mediated C–C Bond Formation

The discovery that Ti(IV) alkoxides can be employed in a simple experimental procedure for the generation of metallacyclopropanes represented perhaps an underappreciated advance in the chemistry of Group 4 metallacycles.[11] While reaction development in this broad area of chemistry was initiated with cyclopentadienyl-based Zr- and Ti- reagents,[12, 13] the observation that related reactivity was accessible from inexpensive and robust Ti-alkoxides, marked what could be referred to as a historic advance in the area. Early attention remained focused on the Kulinkovich reaction as a means to prepare functionalized cyclopropanes from the reaction of Grignard reagents with esters.[14] Later, this general mode of reactivity was expanded to encompass intermolecular variations of this reaction that proceeded by transfer of Ti from a preformed metallacyclopropane to a synthetically valuable terminal alkene.[15] Concurrent with these studies, the basic reactivity patterns of $(RO)_2Ti$–alkyne and $(RO)_2Ti$–imine complexes, reflecting the related chemistry of Cp_2Ti– and Cp_2Zr– complexes, were beginning to emerge.[16]

These early studies served to demonstrate that metallacyclopropanes/propenes, formed by the *in situ* reduction of Ti(IV) alkoxides, were competent organometallic intermediates for metal-centered [2+2+1] chemistry. However, barriers associated with the control of regioselectivity, stereoselectivity, and generally low levels of reactivity in these bimolecular C–C bond forming processes have broadly restricted this, and related areas of reaction development to a relatively modest collection of convergent coupling processes between a limited set of unsaturated substrates.[17]

Only recently have reaction strategies emerged that offer general and highly selective means for the control of intermolecular metal-centered [2+2+1] chemistry.[17] The early observations of Rothwell and Kulinkovich validated that C–C bond formation with Ti-alkoxide-based metallacyclopropanes was viable. Given the well established propensity for Ti(IV) alkoxides to undergo rapid and reversible ligand exchange,[18] and their ability to generate reactive metallacyclopropanes, we have been actively pursuing the development of alkoxide-directed metal-centered [2+2+1] chemistry based on these relatively benign, readily available, inexpensive, and easily handled metal alkoxides. The allylic alcohol–imine coupling reaction described here is a unique bimolecular bond construction that has surfaced from our studies in this area.

Results and Discussion

Our pursuit began with the proposal of a general pathway for Ti-alkoxide-mediated reductive cross-coupling of imines with allylic alcohols (Figure 4).[10a] Formation of a Ti–

imine complex **9**, followed by exposure to an allylic alkoxide **10** would lead to the transient mixed titanate ester **11** by rapid and reversible ligand exchange. Subsequent carbometalation, by way of **12**, would deliver a strained bicyclic azametallacyclopentane (**13**), which has the potential to undergo a *syn*-elimination similar to that postulated in the Tebbe olefination.[19]

If such a sequence were possible, we anticipated that carbometalation would proceed through a boat-like transition state geometry, as in **12**, based on mechanistic assumptions that include: 1) alignment of the σ_{Ti-C} bond with $\pi_{C=C}$ bond, and 2) association of the allylic alkoxide of **10** with Ti to render the carbometalation event intramolecular.[20] Further assuming that the carbometalation (**12** → **13**) would be essentially irreversible,[21] we anticipated that all aspects of stereochemistry associated with product (**3**) would derive from stereochemical control through minimization of non-bonded steric interactions in the boat-like transition state **12**.[22] Interestingly, complexities with this process emerge from a cursory inspection of this proposal, as the Ti–imine complex **9** is chiral, and the addition to substituted allylic alcohols (**10**) could be complicated by significant double asymmetric relationships.[23]

We initiated study of the proposed bond construction with the attempted coupling of an aromatic imine with simple allylic alcohols. As illustrated in eq 1 of Figure 5, coupling of imine **14** with allyl alcohol (**15**) delivers homoallylic amine **16** in 70% yield. While we were delighted to observe success in this initial coupling reaction, our enthusiasm was dampened by the host of other methods available for simple allylation of imines.[24] We therefore decided to move on to explore more challenging and unprecedented bond constructions with this novel Ti-mediated coupling reaction.

Imine prenylation remains a challenging problem in reaction methodology, as allylic organometallic reagents typically deliver homoallylic amine products derived from inverse prenylation.[25] Interestingly, as depicted in eq 2 of Figure 5, Ti-alkoxide-mediated coupling of imine **14** with the tertiary allylic alcohol **17** proceeds with exquisite levels of regioselection to deliver the product of prenylation **18** in 83% yield. In this process, no evidence could be found for the production of isomeric homoallylic amine products (rs ≥ 20:1). This impressive level of regioselection can be extended to the production of homoallylic amines bearing a tetrasubstituted alkene. As depicted in eq 3, coupling of imine **14** with allylic alcohol **19** delivers **20** in 80% yield, again with high regioselection (≥ 20:1).

While initial reports documenting the conversion of imines to azatitanacyclopropanes with $Ti(O\textit{i}\text{-}Pr)_4$ were limited to a small subset of aromatic imines, subtle perturbation of the established reaction conditions defined a pathway to employ aliphatic imines in this reductive cross-coupling reaction.[26] Simply replacing the Grignard reagent typically employed to access the initial "low-valent" Ti-species with *n*-BuLi provides a set of conditions suitable to extend this mode of reactivity to aliphatic imines. While we are uncertain of the mechanistic underpinnings that allow for success in these transformations, imine prenylation of branched (**21**) and unbranched (**23**) imines proceed in ≥ 80% yield and deliver products as single regioisomers (eqs 4 and 5).

Next, we shifted our attention to the examination of relative stereochemistry in the coupling of achiral imines with achiral allylic alcohols bearing an internal alkene. Coupling of imine **14** with the (*E*)-allylic alcohol **25** delivers homoallylic amine **26** in 87% yield (Figure 6A, eq 6). Here, the regioselective allyl transfer reaction is coupled to very high levels of diastereoselection that favor the formation of the *anti*- product (ds ≥ 20:1). In the related example depicted in eq 7, coupling of imine **14** to the isomeric (*Z*)-allylic alcohol **27** also furnishes homoallylic amine **26** with very high levels of stereoselection, albeit with slightly

diminished yield (68%). This stereoconvergence, whereby each alkene isomer **25** and **27** furnishes the same *anti*-product **26**, is consistent with an empirical model that is based on the minimization of non-bonded steric interactions in the boat-like transition state geometries **A** and **B** (Figure 6B). The isomeric transition states **C** and **D** suffer from the buildup of significant non-bonded steric interactions as a result of the eclipsing of Me- and Ph- substituents about the developing C–C bond.

Moving on, we explored the potential of this allylic alcohol–imine coupling process for the establishment of homoallylic amines bearing stereodefined alkenes.[27] As depicted in eq 8 of Figure 7A, coupling of imine **14** with allylic alcohol **28** provides the stereodefined homoallylic amine **29** in 87% yield. Here, the highly regioselective coupling process proceeds with exquisite levels of selectivity for the formation of a (*Z*)-trisubstituted alkene (*Z:E* ≥ 20:1). Unfortunately, union of **14** with **30** did not proceed in a similarly selective manner (eq 9). While this coupling reaction delivers homoallylic amines in 92% yield, with very high levels of regio- and *anti*-selectivity, the homoallylic amine products are formed as a 1.6:1 mixture of alkene isomers, favoring the (*Z*)-isomer **31**. Interestingly, the related coupling reaction of **14** with the isomeric allylic alcohol **32** does proceed in a highly selective manner, and delivers homoallylic amine **33** in 57% yield (eq 10). Here, highly regioselective C–C bond formation occurs in concert with the establishment of an anti-homoallylic amine possessing an (*E*)-disubstituted alkene (*anti:syn* ≥ 20:1; *E:Z* ≥ 20:1).

In a similarly impressive example, coupling of imine **14** with the trisubstituted allylic alcohol **34** provides the stereodefined homoallylic amine **35** in 54% yield (eq 11). Here, regioselective coupling again occurs to deliver a homoallylic amine possessing an *anti*-stereochemical relationship, yet this time it does so while establishing a (*Z*)-trisbustituted alkene with high levels of stereocontrol (≥ 20:1).

The reactions depicted in Figure 7A are quite complex and deserve further comment. All allylic alcohols employed in these reactions were racemic, and formation of the Ti–imine complex of **14** occurs without stereochemical bias. As a result, all of these coupling reactions are complicated by the potential of diastereomeric combinations of metallacyclopropane and allylic alcohol [i.e. (*R*)-imine complex + (*R*)-**28** vs (*R*)-imine complex + (*S*)-**28**]. Nevertheless, the results of these experiments are consistent with an empirical model that is based on: 1) *in situ* interconversion of azatitanacyclopropane enantiomers,[28] 2) kinetically controlled carbometalation,[21] and 3) *syn*-elimination through a boat-like transition state geometry. As depicted in Figure 7B, coupling reactions of (*Z*)-allylic alcohols are reasoned to be (*E*)-selective via reaction by way of a transition state geometry **E**, where minimization of A-1,3 strain[29] results in an equatorial disposition of the allylic substituent (R). If this stereoselective carbometalation is followed by *syn*-elimination, then the equatorial disposition of this group results in the formation of the (*E*)-alkene of **33**. The high *anti*-selectivity observed in the formation of **33** is consistent with the minimization of eclipsing non-bonded steric interactions about the developing C–C bond.

Alternatively, in the (*Z*)-selective coupling reactions of **34**, stereoselection is consistent with transition state **F** (Figure 7B). Here, minimization of A-1,2 interactions in a boat-like transition state geometry is reasoned to result in a pseudo-axial disposition of the allylic substituent. As discussed previously, stereoselective carbometalation followed by *syn*-elimination would then furnish the (*Z*)-*anti*-homoallylic amine **35**.

The lack of stereoselection observed in the coupling reaction of the (*E*)-disubstituted allylic alcohol **30**, likely results from the ability of the boat-like transition state geometry to accommodate pseudo-axial or pseudo-equatorial orientations of the allylic substituent without suffering destabilization from significant A-1,2 or A-1,3 strain.

Enantioselective coupling

The high anti-selectivities observed in the reactions of allylic alcohols **30**, **32**, and **34** point to the ability of these coupling reactions to accomplish kinetic resolution. In each case, one enantiomer of the allylic alcohol (**32** or **34**) preferentially reacts with one enantiomer of the Ti–imine complex to afford the *anti*- products.[30] If this were incorrect, then one would anticipate the appearance of *syn*-homoallylic amine products. Their absence in these coupling reactions led us to conclude that coupling reactions of optically active allylic alcohols with racemic Ti–imine complexes would define a means to render this convergent coupling process enantioselective.

As depicted in Figure 8, eqs 12–14, we were delighted to find that coupling reactions of (*R*)-**32** with aromatic and aliphatic imines proceed in a manner to effectively translate stereochemical information from the allylic alcohol starting material to the homoallylic amine products.[31] While these observations are consistent with reasoning derived from analysis of the reactions depicted in Figure 7A, we realized that a central feature of the enantioselective reactions depicted in eqs 12–14 was the translation of stereochemical information from the allylic alcohol to the azametallacyclopropane through the minimization of eclipsing interactions about the developing C–C bond (see the positioning of the highlighted Me- and Ph substituents in **E** and **F** of Figure 7B). We wondered whether this control feature is necessary for the enantioselective version of this convergent coupling reaction. As such, we examined the coupling of the enantioenriched allylic alcohol (*R*)-**28** (80% ee); a substrate that lacks terminal substitution of the alkene. While this coupling reaction did proceeded in an enantioselective fashion, significant erosion of optical purity was observed for homoallylic amine product **29** (46% ee).

These studies (focused on stereochemistry) provided support that the present Ti-mediated allylic alcohol–imine coupling can proceed in a highly controlled manner. Alongside these efforts, we have broadly explored functional group compatibility associated with this reductive cross-coupling reaction. Due to the wealth of reactivity available with vinyl- and aromatic halides, we initiated studies to explore the compatibility of the allylic alcohol–imine coupling reaction with substrates harboring this functionality. As depicted in Figure 9A, allylic alcohols that contain vinyl chlorides, bromides and iodides are all compatible with the coupling process. [10a, 32] Recently, the orthogonality of this Ti-mediated coupling process with vinyl halides was employed to define a simple one-pot process for the stereoselective synthesis of exo-alkylidene γ-lactams (Figure 9B).[32]

This allylic alcohol–imine reductive cross-coupling reaction is also compatible with allylic silanes. As illustrated in Figure 10, orthogonality of this formal allyltransfer process to the chemistry of allylsilanes,[10a, 33] was demonstrated in a reaction sequence of utility for the formation of stereodefined heterocycles. This complex example, also revealing the compatibility of indoles and acetals in the Ti-mediated coupling process, delivers the stereodefined polycyclic heterocycle **43** (dr ≥ 20:1), in just two steps from allylic alcohol **40** and imine **41**.

Double Asymmetric Coupling Processes

Overall, the Ti-mediated allylic alcohol–imine coupling process has been demonstrated to be a powerful convergent coupling reaction, being compatible with a range of functional groups and offering control over regioselection, relative stereochemistry (allylic and homoallylic positions), and olefin geometry. As depicted in Figure 11, coupling reactions have proven useful for the stereoselective synthesis of *anti*-homoallylic amines possessing (*E*)-disubstituted (eq 16), and "(*Z*)"-trisubstituted olefins (eq 17). While a related coupling reaction did produce an *anti*-homoallylic amine bearing a (*Z*)-disubstituted alkene (eq 18)

(*anti:syn* ≥ 20:1), this process did not proceed with very high levels of stereochemical control (*Z:E* = 1.6:1). In addition to these observations concerning relative stereochemical control, we have been successful in defining a highly enantioselective cross-coupling reaction (eq 19). Unfortunately, asymmetric coupling of a simple 1,1-disubstituted olefin with an achiral imine does not proceed with good translation of optical purity (eq 20). In an effort to overcome the limitations in stereochemical control observed from these studies (i.e. eq 18 and 20), we directed our attention to the study of double asymmetric reductive cross-coupling reactions.

While it was straightforward to prepare enantiodefined allylic alcohols suitable for these studies, the selection of an appropriate chiral imine was more complicated. As illustrated in Figure 12, chiral substituents could be introduced by modification of R^3, R^4, or both. We selected to pursue installation of a chiral auxiliary at R^3 as a general means to control formation of the chiral azametallacyclopropane reaction partner. This choice was made based on previous success in Zr- and Ti-mediated coupling reactions of imine **44** with TMS-acetylene (Figure 13). First reported in the Zr-promoted reaction by Taguchi, imine **44** could be converted to the chiral allylic amine **45** with very high levels of stereoselection (ds = 95:5; obtained after heating the preformed azametallacyclopropane to 70 °C prior to addition of the alkyne).[34] Later, in 2003, Sato demonstrated that bond construction can be promoted at low temperature with a Ti-alkoxide reagent, providing **45** with similarly high levels of stereoselection (dr > 97:3).[35]

As depicted in Figure 14, the double asymmetric reductive cross-coupling between imine **44** and a range of chiral (*E*)-allylic alcohols proved to be quite effective in preparing (*Z*)-*anti*-homoallylic amine products (eqs 24–27). This reaction is also compatible with chiral imines derived from aliphatic aldehydes. As illustrated in eq 28, reductive cross-coupling imine **55** with allylic alcohol **53** proceeds in 60% yield, and delivers the stereodefined hoimoallylic amine **56** with very high levels of stereocontrol (*Z:E* ≥ 95:5; *anti:syn* ≥ 95:5).

Interestingly, changing the absolute stereochemistry of the imine coupling partner results in a unique stereoselective bond construction. As depicted in eq 29 (Figure 14), reaction of *ent*-**44** with **47** delivers the *syn*-homoallylic amine **57**, albeit with only modest levels of stereoselection (**57:58** = 2.3:1).

The sum of the experiments depicted in Figure 14 defines a substantial double asymmetric relationship in these Ti-mediated allylic alcohol–imine reductive cross-coupling reactions. The stereochemical pairing in eqs 24–27 clearly represent matched double asymmetric reactions, while that depicted in eq 28 represents a mismatched double asymmetric relationship.

An empirical model for these complex coupling reactions is depicted in Figure 15. As has been previously proposed, chirality transfer from the phenylglycine auxiliary to the azametallacyclopropane likely results from two factors: 1) coordination of the pendant methyl ether to Ti, and 2) minimization of non-bonded steric interactions inside the resulting *cis*-fused bicyclo[3.1.0] system (Figure 15A). As depicted in Figure 15B, assuming that ligand exchange (Ti–O bond formation) is required prior to carbometalation, the matched and mismatched transition state geometries may resemble **A** and **B**. If these models were correct, then they would seem to imply that the alkyl substituent (R) is best accommodated in a position oriented toward the developing C–C bond. While it is not yet possible to conclude that this is a preferred orientation of the allylic substituent, we searched for an alternative explanation, as we could not find a compelling argument to support this proposition.

If instead, the carbometalation could proceed prior to ligand exchange, with association occurring by a different Lewis acid–Lewis base interaction, then one could imagine reaction through a conformation consistent with the "inside alkoxy effect."[36] As depicted in Figure 15C, the matched double asymmetric pairing could then occur through a geometry similar to **C**, where the allylic substituent (R) is preferentially disposed away from the developing $\sigma_{Ti–C}$ bond. In a similar fashion, the mismatched pair could react through a related geometry (**D**). Here, while the allylic moiety (R) is positioned anti to the developing $\sigma_{Ti–C}$ bond, this relationship requires that the transition state suffer from the build up of significant non-bonded steric interactions about the developing C–C bond. We propose these models to provide a tool to aid in the selection of appropriate reaction partners for this complex convergent coupling process and recognize that future computational studies may aid in both refining their structure and assessing their validity.

Finally, in an effort to overcome the low levels of stereoinduction in the asymmetric coupling of chiral 1,1-disubstituted olefins with achiral imines, we pursued a modified version of this process to deliver (*Z*)-homoallylic amines with high levels of stereocontrol. As illustrated in Figure 16, eq 30, coupling of the chiral imine ***ent*-44** with the racemic allylic alcohol (+/−)-**28** proceeded in a highly stereoselective fashion and delivered **59** in 89% yield. With (+/−)-**28** as the limiting reagent, success in this process indicates the ability of each enantiomer to react with the chiral complex of ***ent*-44** in a stereoconvergent manner.

Conclusion

With our focus on the discovery and elaboration of unique metal-centered [2+2+1] chemistry for convergent C–C bond formation, we have discovered a series of stereoselective Ti-mediated reactions for the union of allylic alcohols with imines. During the course of our study, we have found that Ti-mediated coupling reactions of allylic alcohols with imines offers a family of bond constructions that are unrivaled by existing chemical methods. Moving beyond the study of simple allylation, our studies have realized: 1) a highly regioselective allylic alcohol-based coupling reaction, 2) a general pathway for imine prenylation, 3) a means for the establishment of *anti*-homoallylic amines in concert with the stereoselective generation of (*E*)- or (*Z*)-alkenes, and 4) enantioselective formation of complex homoallylic amines via single- or double-asymmetric reaction manifolds. Finally, a series of empirical models have been proposed for these complex bimolecular C–C bond forming processes that are consistent with the sense of regio- and stereoselection observed. Due to the low cost of the metal-containing reagents,[37] the ready availability of the coupling partners, benign nature of the byproducts (TiO_2 and Mg(II) salts), and substrate-controlled selectivity, the current fragment coupling process is anticipated to be of great utility in chemical synthesis. We look forward to advances in reaction development and chemical synthesis that follow from this report.

Experimental Section

General procedure for the reductive cross-coupling of aromatic imines with allylic alcohols

Synthesis of (±)-N-benzyl-1-phenylbut-3-en-1-amine (16)—To a solution of imine **14** (125 μL, 131 mg, 0.672 mmol) and Ti(O*i*-Pr)$_4$ (300 μL, 288 mg, 1.01 mmol) in Et_2O (2.5 mL) at −78 °C was added dropwise *c*-C_5H_9MgCl (2.25 M in Et_2O, 2.03 mmol) via a syringe. The mixture was warmed to −40 °C over 30 min and stirred for 1 h at this temperature. A solution of lithium alkoxide, prepared by the deprotonation of alcohol **15** (69 μL, 58.9 mg, 1.01 mmol) in THF (1.0 mL) at −78 °C with *n*-BuLi (2.56 M in hexanes, 1.08 mmol) followed by warming to 0 °C over 15 min, was added dropwise to the brown solution of imine–Ti complex at −40 °C via cannula. The mixture was warmed to 0 °C over 30 min

then stirred at this temperature for 3 h. The reaction was quenched by addition of H_2O (1.0 mL) followed by rapid stirring until the precipitate became white in color. The mixture was diluted with saturated aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 20 mL). The organic extracts were combined, dried over $MgSO_4$ then concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford homoallylic amine **16** as a colorless oil (112 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.21 (m, 10H), 5.75-5.66 (m, 1H), 5.09-5.02 (m, 2H), 3.71-3.66 (m, 2H), 3.52 (d, *J* = 13.3 Hz, 1H), 2.46-2.36 (m, 2H), 1.75 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1, 140.9, 135.7, 128.6, 128.5, 128.3, 127.5, 127.3, 127.0, 117.7, 61.9, 51.7, 43.3; IR (thin film, NaCl) ν_{max} 3063, 3026, 2835, 1639, 1603, 1585, 1493, 1453, 1356, 1326, 1307, 1198, 1117, 1070, 1028, 995, 916, 824, 759, 700 cm^{-1}; HRMS (EI, H) *m/z* calc'd for $C_{17}H_{20}N$ $[M + H]^+$ 238.1590, found 238.1590.

General procedure for the reductive cross-coupling of aliphatic imines with allylic alcohols

Synthesis of (±)-N-benzyl-2-methylundec-2-en-5-amine (24)—To 6.0 mL of Et_2O at −78 °C was added successively Ti(O*i*-Pr)$_4$ (300 μL, 288 mg, 1.0 mmol) and *n*-BuLi (2.4 M in hexanes, 2.0 mmol). The resulting orange solution was stirred for 10 min, and then imine **23** (203 mg, 1.0 mmol) in THF (1.0 mL) was added in one portion via a syringe. The bright orange solution was allowed to warm to room temperature over 1 h, during which it became deep red-brown. In a separate flask at −30 °C the lithium alkoxide of alcohol **17** (52 μL, 43.1 mg, 0.5 mmol) was generated in THF (0.5 mL) with an equimolar amount of *n*-BuLi, and allowed to warm slowly to 0 °C over 15 min. The orange solution of imine–Ti complex was recooled to −78 °C, and the alkoxide was added dropwise over 5 min. The resulting dark red solution was slowly warmed to room temperature over 12 h, and then saturated aqueous NH_4Cl (0.8 mL) was added dropwise. The resulting blue suspension was stirred for 30 min, filtered, the flask rinsed with EtOAc (2 × 5 mL), and concentrated. The crude product was purified by flash column chromatography on silica gel (1/8 EtOAc/hexanes) to afford homoallylic amine **24** as a colorless oil (252 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.16 (m, 5H), 5.11 (triplet of septets, *J* = 7.2, 1.2 Hz, 1H), 3.77 (s, 2H), 2.55 (m, 1H), 2.13 (t, *J* = 7.2 Hz, 2H), 1.72 (s, 3H), 1.63 (s, 3H), 1.45-1.26 (m, 15H), 0.89 (t, *J* = 7.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 133.6, 128.3, 128.1, 126.7, 121.4, 57.3, 51.4, 34.2, 32.7, 31.9, 29.6, 25.9, 25.8, 22.7, 18.1, 14.1; IR (thin film, NaCl) ν_{max} 3027, 2956, 2926, 2855, 1494, 1454, 1376, 1103, 1028, 729, 697 cm^{-1}; HRMS (EI, H) *m/z* calc'd for $C_{19}H_{32}N$ $[M + H]^+$ 274.2529, found 274.2554.

General procedure for the one-pot synthesis of γ-lactam

Synthesis of (3S*,3aS*)-2-benyl-3-phenyl-2,3,3a,4,5,6-hexahydro-1H-isoindol-1-one (39)—To a solution of imine **14** (74 μL, 78 mg, 0.400 mmol) and ClTi(O*i*-Pr)$_3$ (1.0 M in Et_2O, 0.500 mmol) in toluene (1.6 mL) at −70 °C was added *c*-C_5H_9MgCl (2.00 M in Et_2O, 1.00 mmol) in a dropwise manner via a syringe. The orange-brown solution was slowly warmed to −40 °C over 30 min and stirred at this temperature for 1.5 h. A solution of sodium alkoxide, prepared by the deprotonation of alcohol **38** (106 mg, 0.600 mmol) in THF (1.6 mL) at 0 °C with NaH (60% dispersion in mineral oil, 30 mg, 0.750 mmol), was added dropwise via cannula to the brown solution of imine–Ti complex at −40 °C. The reaction was allowed to warm to room temperature and stirred overnight. To the reaction was added H_2O (36 μL, 36 mg, 2.00 mmol), and the resultant mixture was rapidly stirred for 2 h.

To the yellow solution of the reaction mixture was added $PdCl_2$ (1 mg, 0.008 mmol), *t*-Bu_3P (1.0 M in toluene, 0.024 mmol), and Et_3N (223 μL, 161 mg, 1.60 mmol). The reaction was placed under an atmosphere of carbon monoxide using a balloon, and heated at 70 °C for 12 h. After cooling down to room temperature, the mixture was diluted with EtOAc (10 mL)

and filtered through a pad of Celite. The filtrate was further diluted with EtOAc (75 mL) and washed successively with 1.0 N HCl aqueous solution (75 mL), saturated aqueous $NaHCO_3$ (75 mL), and brine (100 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (1/10 → 1/5 EtOAc/hexanes) to afford γ-lactam **39** as a white solid (89 mg, 73%, dr ≥ 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.22 (m, 3H), 7.18-7.10 (m, 3H), 7.10-7.05 (m, 2H), 6.94-6.86 (m, 2H), 6.54 (dt, *J* = 3.3, 3.3 Hz, 1H), 5.04 (d, *J* = 14.4 Hz, 1H), 3.78 (d, *J* = 7.6 Hz, 1H), 3.50 (d, *J* = 14.4 Hz, 1H), 2.54-2.40 (m, 1H), 2.28-2.14 (m, 1H), 1.85-1.66 (m, 2H), 1.43-1.26 (m, 1H), 1.16-0.99 (m, 1H); NMR (100 MHz, $CDCl_3$) δ 169.2, 139.3, 136.5, 134.9, 129.0, 128.8, 128.5, 128.3, 127.6, 127.4, 66.7, 45.3, 44.4, 25.1, 24.8, 21.5; IR (thin film, NaCl) ν_{max} 3026, 2929, 2862, 1688, 1494, 1455, 1393, 1272, 736, 701 cm^{-1}; HRMS (EI, H) *m/z* calc'd for $C_{21}H_{22}NO$ $[M + H]^+$ 304.1696, found 304.1666.

General procedure for the synthesis of quinolizidines and indolizidines

Synthesis of (8S*,11S*,11aS*)-5,11-dimethyl-10-methylene-8-(thiophen-2-yl)-5,6,8,9,10,11,11a,12-octahydroindolo[3,2-b]quinolizine (43)—To a solution of imine **41** (295 mg, 0.86 mmol) in Et_2O (10 mL) was added $Ti(Oi\text{-}Pr)_4$ (390 μL, 366 mg, 1.29 mmol). After stirring for 10 min, the solution was cooled down to −78 °C and *c*-C_5H_9MgCl (2.0 M in Et_2O, 2.58 mmol) was added via a syringe over 2 min. The solution turned from yellow to dark brown after stirring at −78 °C for 1.5 h. Next, a solution of lithium alkoxide, prepared by the deprotonation of alcohol **40** (201 mg, 1.29 mmol) in THF (2.0 mL) at −78 °C with *n*-BuLi (2.5 M in hexanes, 1.37 mmol) followed by stirring for 10 min, was added dropwise to the brown solution of imine–Ti complex via cannula. The mixture was slowly warmed to room temperature, and stirred for 16 h. The reaction was quenched by sequential addition of Et_2O (10 mL) and saturated aqueous $NaHCO_3$ (5 mL), followed by vigorous stirring for 1 h. The aqueous phase was extracted with Et_2O (2 × 10 mL). the organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (1/20 EtOAc/hexanes) to afford homoallylic amine **42** as a yellow oil (290 mg, 70%).

To a solution of homoallylic amine **42** (56 mg, 0.12 mmol) in THF (5 mL) was added 1.0 N HCl aqueous solution (0.5 mL, 0.5 mmol). After stirring for 16 h, the reaction was quenched by addition of pulverized K_2CO_3 (150 mg, 1.1 mmol). The neutralized mixture was extracted with Et_2O (2 × 10 mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (1/40 EtOAc/hexanes) to afford quinolizidine **43** as a white solid (26 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.2 Hz, 1H), 7.18 (m, 1H), 7.14 (m, 1H), 6.98 (m, 1H), 6.91 (m, 2H), 6.89 (m, 1H), 4.73 (s, 1H), 4.60 (s, 1H), 3.99 (ABq, *J* = 14.8 Hz, 1H), 3.61 (dd, *J* = 11.6, 3.6 Hz, 1H), 3.12 (ABq, *J* = 14.8 Hz, 1H), 3.04 (dd, *J* = 12.4, 10.4 Hz, 1H), 2.80 (dd, *J* = 13.6, 12.0 Hz, 1H), 2.75 (m, 1H), 2.70 (dd, *J* = 14.8, 3.6 Hz, 1H), 2.55 (qd, *J* = 6.4, 2.8 Hz, 1H), 2.29 (dd, *J* = 13.6, 2.8 Hz, 1H), 1.29 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 148.6, 137.2, 132.4, 126.4, 126.2, 124.7, 124.2, 120.7, 118.8, 117.8, 108.6, 106.2, 68.1, 62.5, 50.4, 42.2, 41.3, 29.1, 26.0, 14.8; IR (thin film, NaCl) ν_{max} 3585, 2919, 1660, 1471 cm^{-1}; LRMS (ESI, H) *m/z* calc'd for $C_{22}H_{25}NOS$ $[M + H]^+$ 412.2, found 412.5.

General procedure for the double asymmetric cross-coupling of phenylglycine-derived imines with chiral allylic alcohols

Synthesis of (1R,2R,Z)-N-((R-2-methoxy-1-phenylethyl)-2-methyl-1-phenylhex-3-en-1-amine (48)—To a solution of imine **44** (239 mg, 1.0 mmol) and $Ti(Oi\text{-}Pr)_4$ (444 μL, 426 mg, 1.5 mmol) in Et_2O (4 mL) at −78 °C was added dropwise *c*-C_5H_9MgCl (2.0 M in Et_2O, 3.0 mmol) via a syringe. The mixture was warmed to −30 °C

over 30 min and stirred at this temperature for another 3 h. A solution of lithium alkoxide **47** in Et_2O (0.5 mL), generated *in situ* via deprotonation of the corresponding alcohol (50 mg, 0.5 mmol) with *n*-BuLi (2.54 M in hexanes, 0.55 mmol) at −78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine–Ti complex at −30 °C via cannula. The resulting mixture was warmed to ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (3% EtOAc/hexanes) to afford homoallylic amine **48** as a pale yellow oil (dr ≥ 20:1, Z:E ≥ 20:1, 126 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-6.96 (m, 10H), 5.45 (app dt, *J* = 10.8, 7.3 Hz, 1H), 5.13 (dd, *J* = 10.8, 10.8 Hz, 1H), 3.67 (dd, *J* = 6.7, 4.7 Hz, 1H), 3.44-3.34 (m, 2H), 3.28 (d, *J* = 8.5 Hz, 1H), 3.26 (s, 3H), 2.72-2.60 (m, 1H), 2.35 (br, 1H), 2.08-1.97 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H), 0.63 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 142.2, 133.3, 133.1, 128.7, 128.0, 127.8, 127.7, 126.8, 126.7, 76.6, 67.5, 61.0, 59.1, 38.8, 21.2, 18.1, 14.6; IR (thin film, NaCl) ν_{max} 3320, 3063, 2962, 2874, 2823, 1946, 1806, 1602, 1493, 1455, 1194, 1110, 757, 698 cm^{-1}; HRMS (ESI, H) *m/z* calc'd for $C_{22}H_{30}NO$ $[M + H]^+$ 324.2327, found 324.2317; $[\alpha]_D^{20}$ +19.8 (*c* 0.69, $CHCl_3$).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge financial support of this work by the National Institutes of Health (GM80266 and GM80266-S1).

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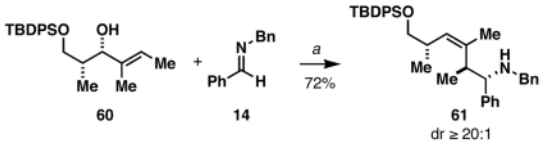
31. Note that the %ee of homoallylic amine products (eqs 12–14) reflect the %ee of the allylic alcohol starting materials. While we were also successful at accomplishing asymmetric coupling between a chiral allylic alcohol possessing a trisubstituted alkene [(*R*)- **34**] and imine **14**, we were unable to establish the ee of the homoallylic amine product by HPLC or derivatization (this coupling reaction proceeded in 77% yield). Given the likely mechanistic course of this coupling reaction, and our inability to identify a minor isomer, the transfer of stereochemical information in this process is reasoned to be as high as that depicted in eq 12. This expectation is in accord with a the highly diastereoselective coupling of imine **14** with the chiral allylic alcohol **96** which occurred with superb levels of diastereoselectivity:[10a]

*Demonstrationg high translation of stereochemical information with a substrate containing a trisubstituted olefin of similar substitution to **34**.*



Reaction conditions: *a)* imine (2 equiv), $Ti(O\textit{i}\text{-}Pr)_4$ (3.1 equiv), *c*-C_5H_9MgCl (6.2 equiv) Et_2O (–78 °C to –40 °C), then and add lithium alkoxide of **60** (1 equiv) in THF (–40 °C to rt), then quench with H_2O.

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35. Fukuhara K, Okamoto S, Sato F. Org Lett. 2003; 5:2145. [PubMed: 12790550]
36. Houk KN, Moses SR, Wu YD, Rondan NG, Jäger V, Schohe R, Fronczek FR. J Am Chem Soc. 1984; 106:3880.
37. For a discussion in the context of regioselective reductive cross-coupling reactions of disubstituted alkynes, see ref 17.

Figure 1.
State-of-the-art methods for allyl transfer via the intermediacy of allylic organometallic reagents.

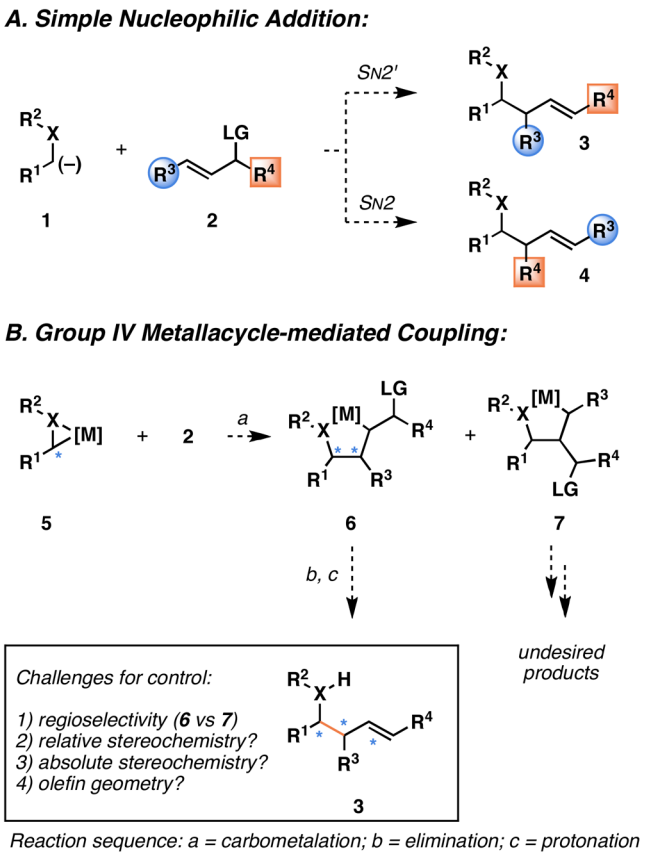


Figure 2.
Umpolung-based strategy for carbonyl allylation.

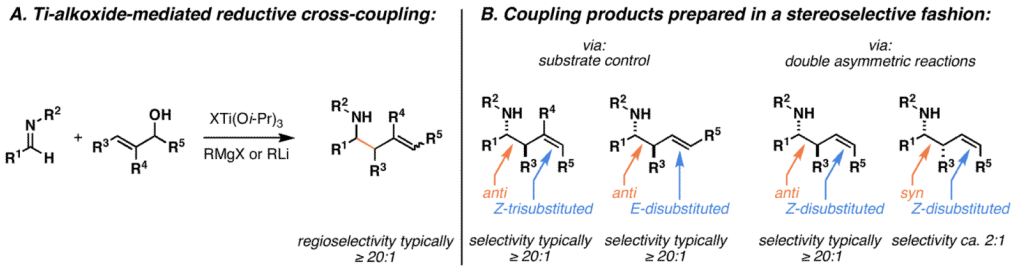


Figure 3.
Homoallylic amines by Ti-alkoxide-mediated reductive cross-coupling.

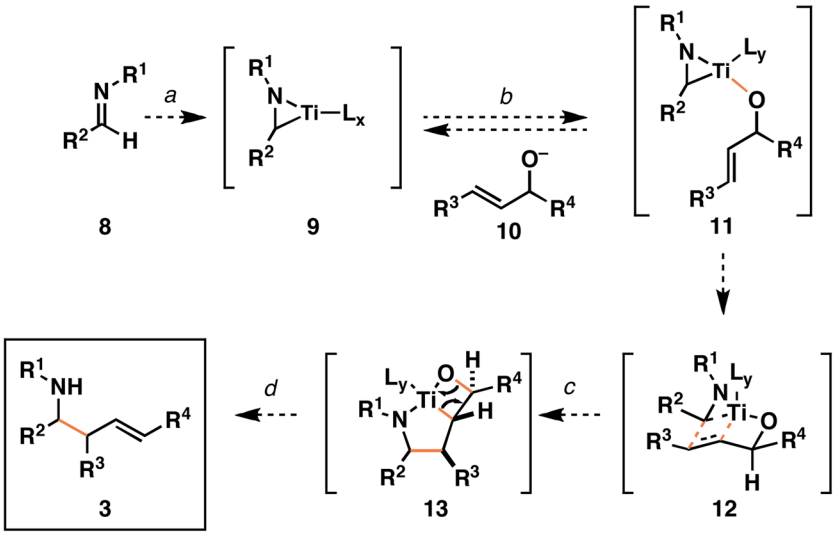
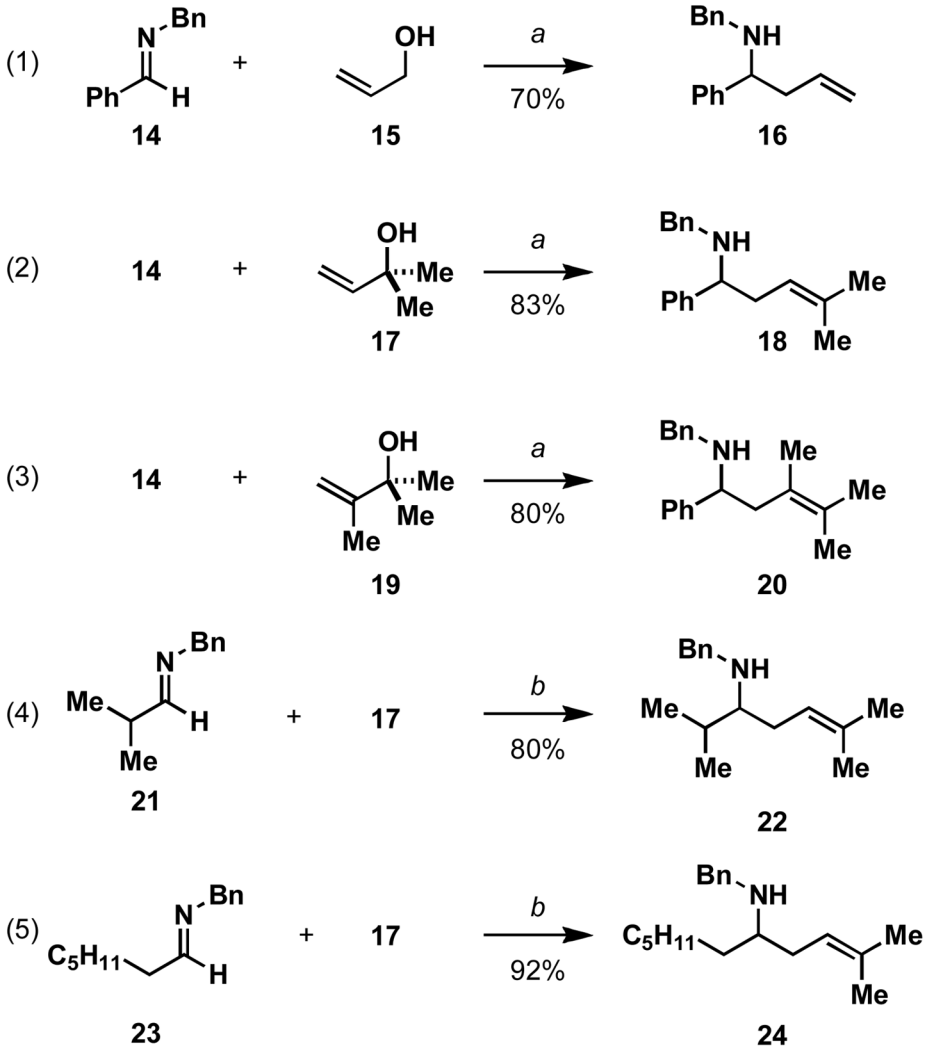


Figure 4.
General strategy for Ti-alkoxide-mediated coupling of allylic alcohols with imines.



[a]Reaction conditions: imine (1 equiv), Ti(O*i*-Pr)$_4$ (1.5 equiv), *c*-C_5H_9MgCl (3 equiv), Et_2O, then add allylic alkoxide (1.5 equiv). [b]Reaction conditions: imine (2 equiv), Ti(O*i*-Pr)$_4$ (2 equiv), *n*-BuLi (4 equiv), Et_2O, then add allylic alkoxide (1.0 equiv).

Figure 5.
Allyl and prenyl transfer chemistry.

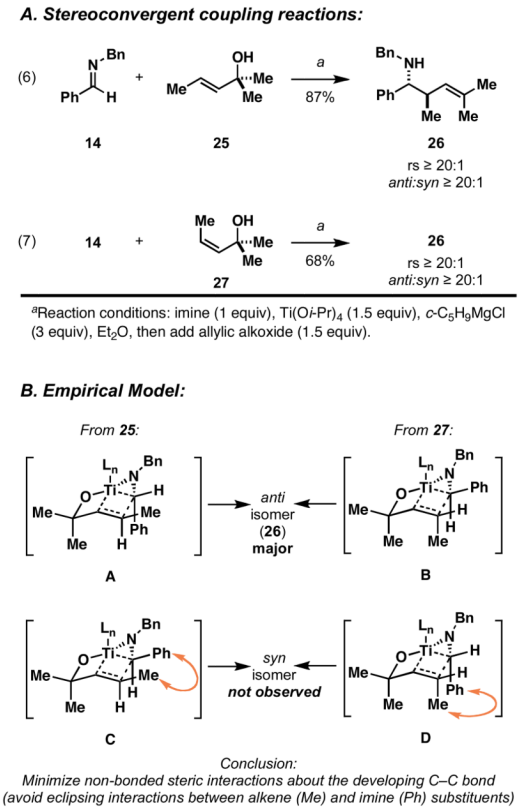


Figure 6.
Simple diastereoselection.

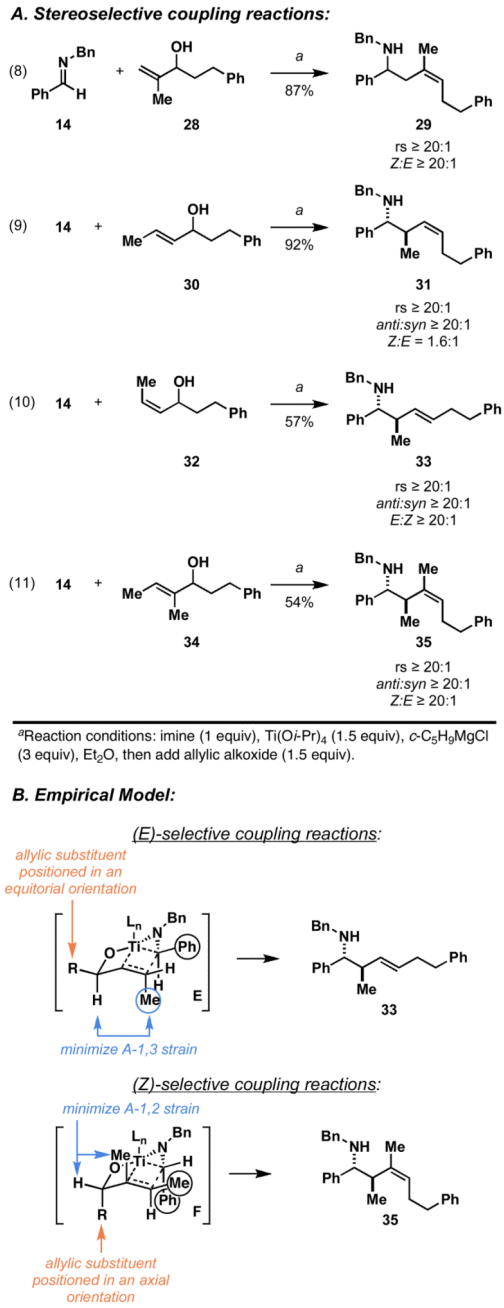
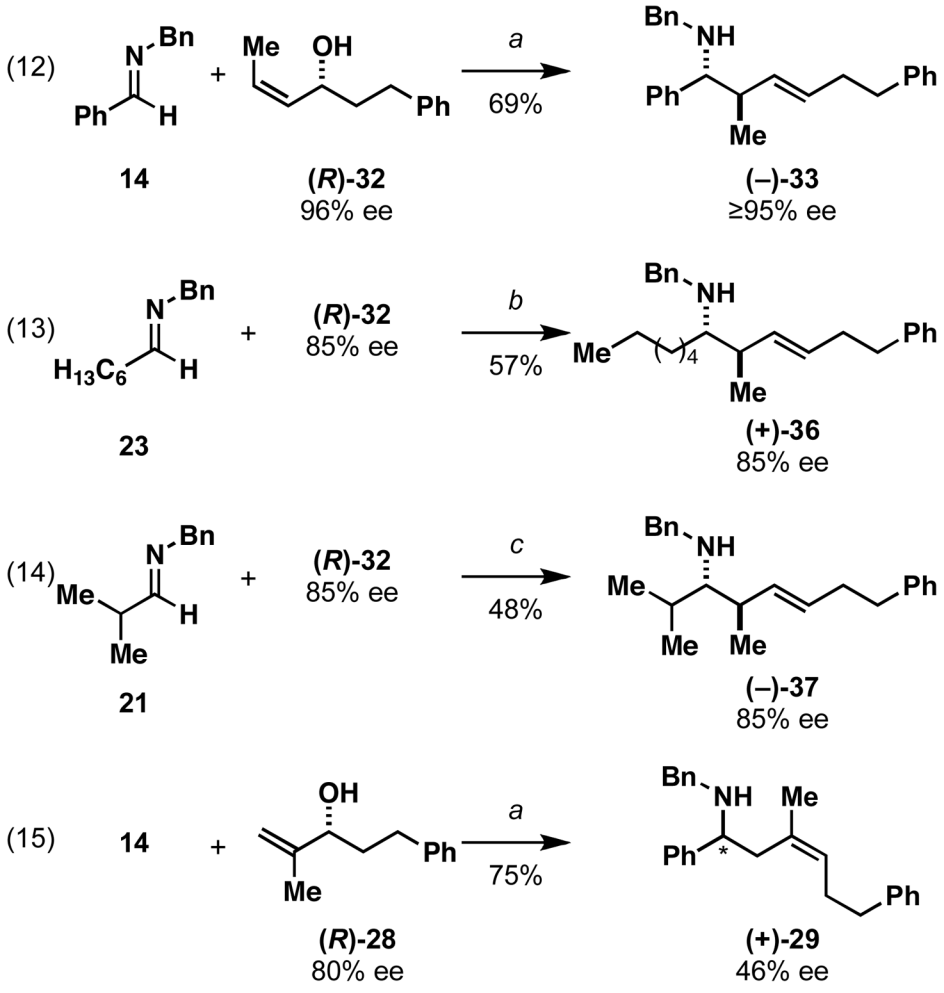


Figure 7.
Allylic alcohol–imine coupling reactions that establish stereodefined di- and tri-substituted alkenes.



Reaction conditions: [a] imine (2 equiv), Ti(O*i*-Pr)$_4$ (3 equiv), *c*-C_5H_9MgCl (6 equiv), Et_2O, then add allylic alkoxide (1 equiv). [b] imine (4 equiv), Ti(O*i*-Pr)$_4$ (4 equiv), C_4H_9MgCl (8 equiv), Et_2O, then add allylic alkoxide (1 equiv). [c] imine (3 equiv), Ti(O*i*-Pr)$_4$ (3 equiv), C_4H_9MgCl (6 equiv), Et_2O, then add allylic alkoxide (1 equiv).

Figure 8.
Enantioselective allylic alcohol–imine coupling.

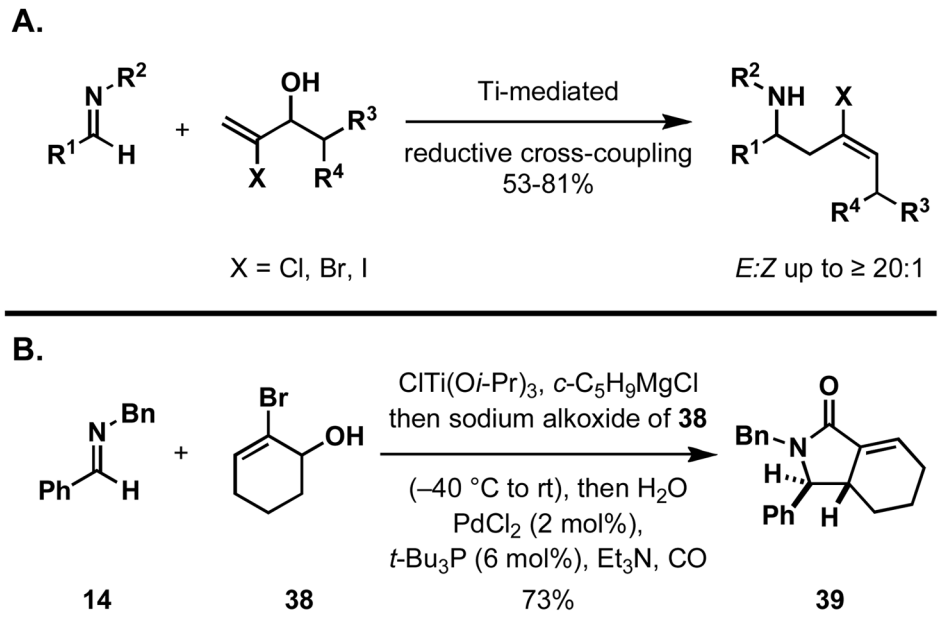


Figure 9.
A one-pot annulation for the synthesis of stereodefined exo-alkylidene γ-lactams.

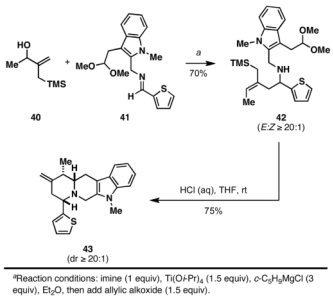


Figure 10.
Convergent synthesis of complex heterocycles via Ti-mediated coupling of allylic alcohols with imines.

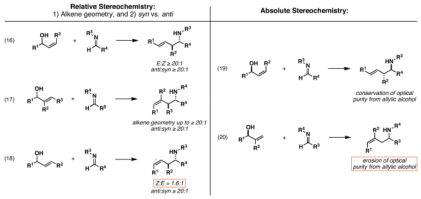


Figure 11.
Summary of stereochemical observation.

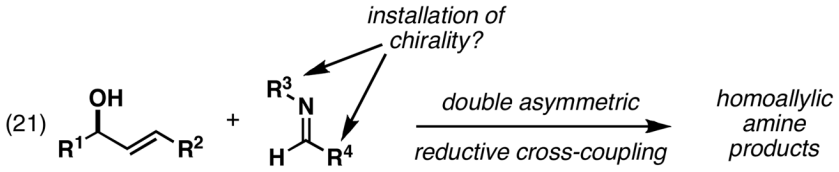


Figure 12.
Potential double asymmetric coupling reactions.

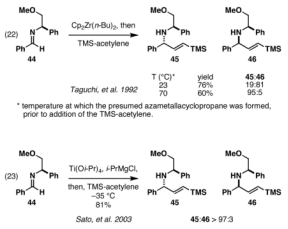


Figure 13.
Use of a phenylglycine auxiliary in azametallacyclopropane-based coupling reactions.

Figure 14.
Double asymmetric reductive cross-coupling.

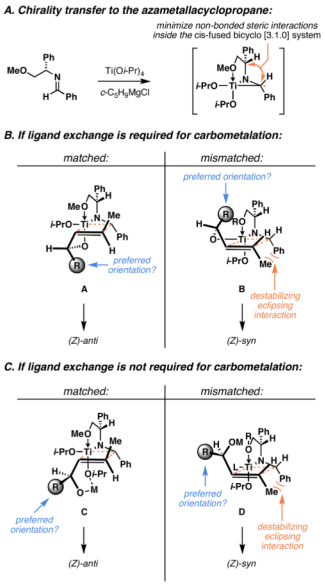


Figure 15.
Empirical model for double asymmetric allylic alcohol–imine reductive cross-coupling.

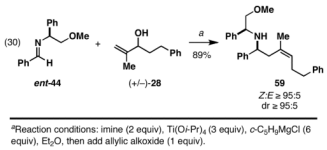


Figure 16.
Stereoselective coupling for the synthesis of chiral (*Z*)-trisubstituted homoallylic amines.