Synthetic Methods

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Complex Allylation by the Direct Cross-Coupling of Imines with Unactivated Allylic Alcohols**

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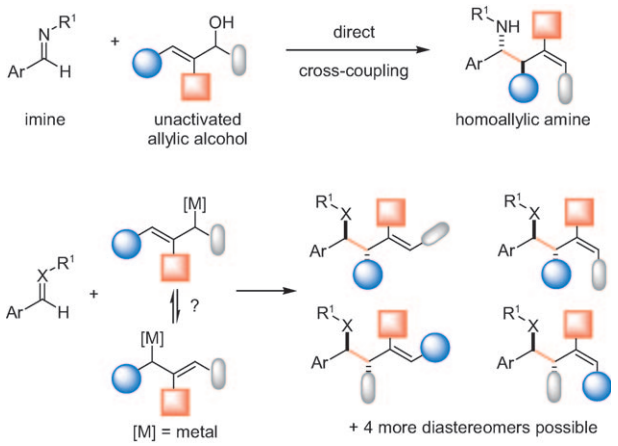
Since the birth of the field, convergent C–C bond-forming reactions have defined the backbone of organic synthesis.[1] While significant advances in reaction development have recently been made in the area of catalysis,[2] contributions that describe novel bimolecular C–C bond construction remain central to the evolution of organic synthesis. Such contributions provide new paradigms for molecular assembly, greatly facilitating the manner in which complex molecules are made. Herein, we describe a convergent coupling reaction between allylic alcohols and imines that delivers complex homoallylic amines with high levels of regio- and stereoselectivity by a pathway that proceeds without the intermediacy of allylic organometallic reagents (Scheme 1, top).

Over the last thirty years, allylation has emerged as a particularly powerful bimolecular C–C bond-forming process, with current examples demonstrating the ability to achieve enantio- and diastereoselective allyl, crotyl, and prenyl transfer.[3] While powerful, the typical dependence on allylic organometallic reagents often restricts the utility of these processes, limiting them to the addition of these simple hydrocarbon fragments.[4] The synthesis and application of more functionalized allylic organometallic reagents for convergent coupling is complicated and typically unwieldy owing to: 1) Functional group tolerance in the preparation of the allylic organometallic reagent, 2) challenges associated with the control of site selectivity in the metalation step, 3) difficulties in controlling site-selective C–C bond formation (resulting from the competition between α vs. γ attack and the known propensity for allylic isomerization of the intermediate organometallic reagent), and 4) problems associated with attaining selectivity in both the establishment of a stereodefined alkene and the tetrahedral stereochemistry at the allylic and homoallylic positions (Scheme 1, bottom). In cases where the allylic metal reagent is generated in a catalytic fashion, functional group tolerance is often enhanced, but complexities still remain because of competing isomerization (of the allylic metal species) as well as the previously mentioned issues with regio- and stereoselection in the C–C bond-forming event.[5] As such, the potential impact of the bond constructions made possible with allylic organometallic reagents (independent of whether such processes are rendered catalytic in the metal) remains limited.



Scheme 1. Allylation for convergent C–C bond formation. Top: Complex allylation without allylic organometallic reagents. Bottom: Allylation with allylic organometallic reagents.

Recent contributions from our laboratory have focused on harnessing the power of metallacycle-mediated C–C bond formation for new convergent coupling reactions in organic chemistry.[6] These accomplishments have derived from the development of general strategies to control the reactivity of metal–π complexes. In particular, association of neighboring alkoxides with the metal center has played a central role in these processes; these functional groups often complicate other C–C bond-forming reactions.[7] One powerful mode of control is reaction by formal metallo-[3,3] rearrangement.[8] Here, we describe a new stereoselective convergent coupling reaction by formal metallo-[3,3] rearrangement that addresses long-standing problems in allyl-transfer chemistry and defines a pathway for complex allylation of imines that: 1) Proceeds by the direct coupling of allylic alcohols, thereby eliminating the need for preformed allylic organometallic reagents, 2) occurs with diverse functional group tolerance, 3) progresses in a highly regioselective manner with net allylic transposition, 4) delivers homoallylic amines with high

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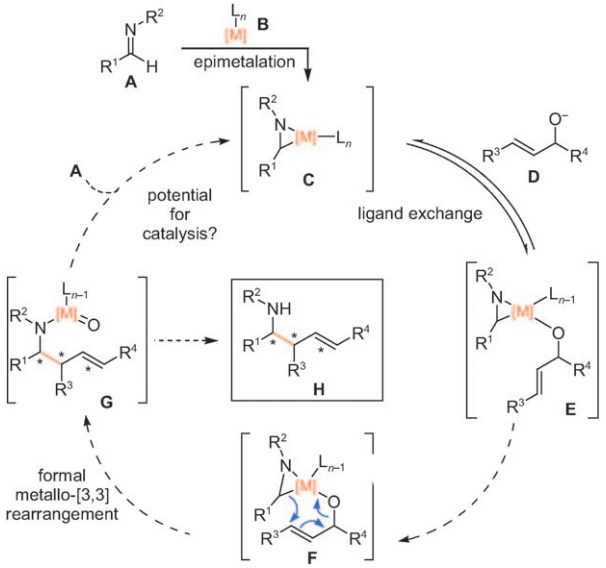
anti selectivity, and 5) establishes a stereodefined di- or trisubstituted alkene in concert with C–C bond formation (Scheme 1, top).

Our generic design for an allylic alcohol–imine cross-coupling process is outlined in Scheme 2. Treatment of an imine (**A**) with a low-valent metal reagent (**B**) was anticipated



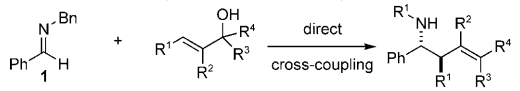
Scheme 2. Reaction design.

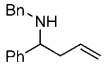
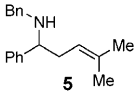
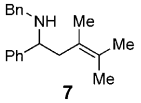
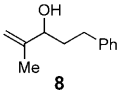
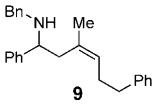
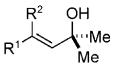
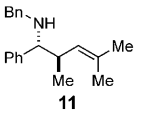
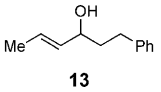
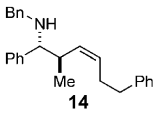
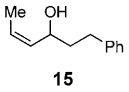
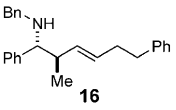
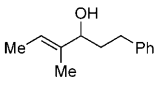
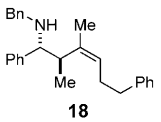
to result in the formation of an intermediate azametallacyclopropane (**C**). Addition of an allylic alkoxide (**D**) to this preformed complex was expected to result in rapid and reversible ligand exchange to deliver **E**. Rearrangement by way of **F** results in the formation of a C–C bond, two stereogenic centers, and one geometrically defined substituted alkene and delivers homoallylic metalated amine **G**. From **G**, simple hydrolysis provides the complex homoallylic amine product **H**. Alternatively, depending on the metal employed, we envisioned a potential pathway for capturing the precious metal intermediate **G** by net reduction and epimetalation with imine **A**. Defining this portion of the reaction would render the process catalytic in the metal component, but was thought to be necessary only if: 1) The reaction requires a complex ligand for control of selectivity (enantio-, diastereo-, or regioselectivity), or 2) the metal employed is rare, expensive, or toxic.

The metal reagent (**B**) selected for this process was a readily available titanium alkoxide, and the control of the coupling reaction was anticipated to follow from the geometrical constraints imposed by reaction through a formal metallo-[3,3] rearrangement. As such, the primary goal of our studies was to investigate the possibility of this stereoselective new bond construction without concern for turning over the nontoxic and readily available titanium alkoxide reagent.

As illustrated in Table 1, coupling of allyl alcohol **2** with imine **1** delivers the simple homoallylic amine **3** in 70% yield (entry 1).[9] With more substituted allylic alcohols (**4** and **6**), coupling provides homoallylic amines bearing proximal tri- and tetrasubstituted alkenes (Table 1, entries 2 and 3); in one

Table 1: Stereoselective synthesis of homoallylic amines.



Entry	Allylic alcohol	Yield [%][a]	*Z*/*E*	d.r.	Product
1	 **2**	70	–	–	 **3**
2	 **4**	83	–	–	 **5**
3	 **6**	80	–	–	 **7**
4	 **8**	87	≥20:1	–	 **9**
					 **11**
5	**10**; R^1 = Me; R^2 = H	81	–	≥20:1	
6	**12**; R^1 = H; R^2 = Me	68	–	≥20:1	
7	 **13**	92	1.6:1	≥20:1[b]	 **14**
8	 **15**	57	≤1:20	≥20:1	 **16**
9	 **17**	54	≥20:1	≥20:1	 **18**

[a] Reaction conditions: See the Supporting Information for details. [b] Each alkene isomer (*Z* and *E*) was identified as the *anti* diastereomer (d.r. ≥ 20:1). Bn = benzyl.

case a useful reaction for the prenylation of aromatic imines is defined (**4**→**5**).[10] Interestingly, coupling of allylic alcohol **8** with imine **1** proceeds with both high regio- and stereoselectivity delivering homoallylic amine **9** in 87% yield as a single geometrical isomer (*Z*/*E* ≥ 20:1; Table 1, entry 4).

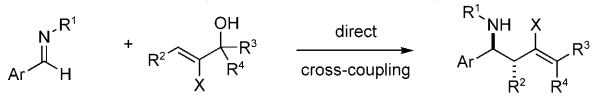
When terminally substituted allylic alcohols are employed, this C–C bond-forming process proceeds in a highly *anti*-selective manner. For example, coupling of either allylic alcohol **10** or **12** with **1** provides the stereodefined product **11** in 81 and 68% yield, respectively (d.r. ≥ 20:1 in both cases; Table 1, entries 5 and 6). With secondary allylic alcohols having geometrically defined alkenes, the control of stereochemistry is more complex, as the challenge of establishing allylic and homoallylic stereochemistry is coupled to the construction of a stereodefined alkene. Nevertheless, reaction of allylic alcohol **13** with **1** provides **14** in 92% yield (*anti*/*syn* ≥ 20:1; Table 1, entry 7). While this coupling reac-

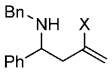
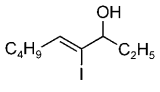
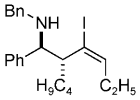
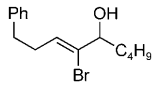
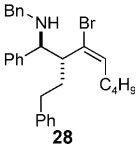
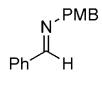
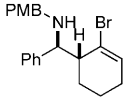
tion does not deliver the stereodefined alkene with high levels of selectivity ($Z/E = 1.6{:}1$), coupling of the isomeric allylic alcohol **15** with **1** delivers **16** with much higher levels of selectivity, favoring the *anti* product with a proximal disubstituted *E* alkene (d.r. $\geq 20{:}1$; $E/Z \geq 20{:}1$; Table 1, entry 8). Finally, coupling of the *E*-trisubstituted allylic alcohol **17** with **1** provides homoallylic amine **18** in 54% yield, in this case delivering the *anti* product with a central *Z*-trisubstituted alkene.

While this convergent coupling reaction affords complex homoallylic amines that are otherwise difficult to prepare, it is also compatible with vinyl halides—a feature that further defines a rather unique stereoselective bond construction for complex molecule synthesis (Table 2). It was found that 2-haloallylic alcohols (**19**–**21**) are suitable substrates for coupling with **1** (Table 2, entries 1–3). In addition, more complex bond constructions are possible in which high *anti* selectivity is coupled to the formation of geometrically defined vinyl halides (d.r. $\geq 20{:}1$; $E/Z \geq 20{:}1$; Table 2, entries 4 and 5). Finally, allylic alcohols bearing carbocyclic vinyl halides are also viable partners in this coupling reaction. Coupling of imine **29** with **30** provides the functionalized cyclohexene **31** in 53% yield (d.r. $\geq 20{:}1$; Table 2, entry 6).

This stereoselective convergent coupling reaction is compatible with a variety of aromatic imines and substituted allylic alcohols. Table 3 highlights the use of this reaction for the synthesis of homoallylic amines bearing heteroaryls (**33** and **38**; entries 1 and 3), tetrasubstituted vinyl halides (**36**; entry 2), aromatic halides (**40**, **42**, and **44**; entries 4–6), additional alkenes (**42** and **44**; entries 5 and 6), as well as a trifluoromethyl-substituted aryl (**40**; entry 4). This reaction can also be extended to ketimines, in this case providing the tertiary carbinolamine **46** in 83% yield (Table 3, entry 7).

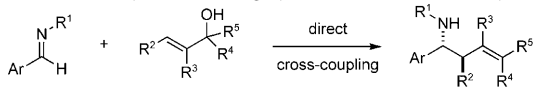
Table 2: Stereoselective synthesis of 3-halohomoallylic amines.

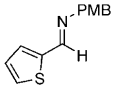
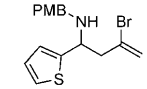
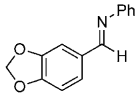
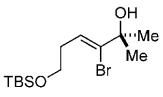
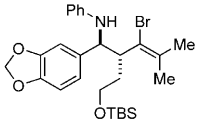
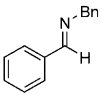
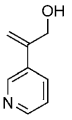
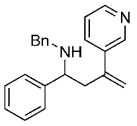
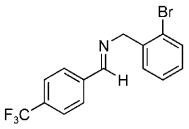
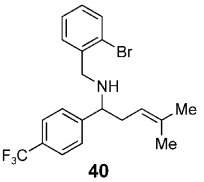
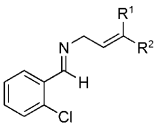
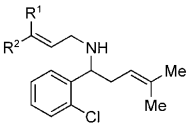
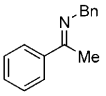
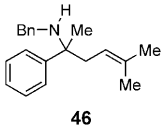
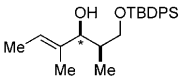
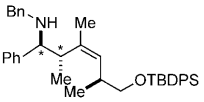


Entry	Imine	Allylic alcohol	Yield [%][a]	*E*/*Z*	d.r.	Product
	 **1**					
1		**19**; X = Cl	59	–	–	**22**; X = Cl
2		**20**; X = Br	61	–	–	**23**; X = Br
3		**21**; X = I	60	–	–	**24**; X = I
4	**1**	 **25**	53	≥20:1	≥20:1	 **26**
5	**1**	 **27**	56	≥20:1	≥20:1	 **28**
6	 **29**	 **30**	53	–	≥20:1	 **31**

[a] Reaction conditions: See the Supporting Information for details. [b] No evidence was found for the production of stereoisomeric products. PMB = *p*-methoxybenzyl.

Table 3: Stereoselective synthesis of highly functionalized homoallylic amines.



Entry	Imine	Allylic alcohol	Yield [%][a]	Product
1	 **32**	 **20**	53	 **33**
2	 **34**	 **35**	52	 **36**
3	 **1**	 **37**	55	 **38**
4	 **39**	 **4**	67	 **40**
5	 **41**; R^1, R^2 = Me	**4**	79	 **42**; R^1, R^2 = Me
6	**43**[c]; R^1 = H, R^2 = CH_2TMS	**4**	69	**44**; R^1 = H, R^2 = CH_2TMS
7	 **45**	**4**	83	 **46**
8	**1**	 **47**	72	 **48** d.r. ≥20:1; *Z*/*E* ≥20:1

[a] Reaction conditions: See the Supporting Information for details. [b] No evidence was found for the production of stereoisomeric products. [c] Compound **43** was used as a mixture of alkene isomers ($E/Z = 4{:}1$). TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl, TMS = trimethylsilyl.

Finally, the absolute stereochemistry of this reaction can be controlled in a substrate-directed manner. Coupling of the stereodefined allylic alcohol **47** with imine **1** provides the chiral stereodefined product **48** in 72% yield, as a single isomer (Table 3, entry 8).[11]

The regiochemical course of this coupling reaction is consistent with an empirical model based on a formal metallo-[3,3] rearrangement via a mixed titanate ester intermediate (Figure 1). The stereochemical control observed is consistent with reaction through a conformation where the $\sigma_{C\text{-}M}$ orbital is aligned with the $\pi_{C=C}$ orbital, while allylic strain (A-1,2/A-1,3) and developing nonbonding 1,2-interactions (**A** and **B**; Figure 1) are minimized.[12]

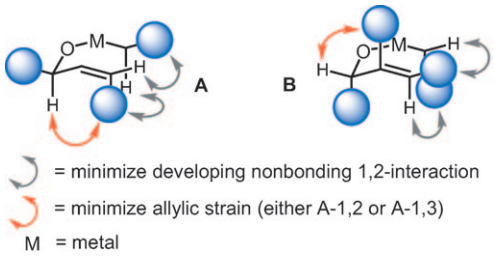


Figure 1. Empirical model for regio- and stereoselection. In conformations **A** and **B** the $\sigma_{C\text{-}M}$ orbital is aligned with the $\pi_{C=C}$ orbital.

In conclusion, we have described a new reaction design to accomplish complex convergent coupling by formal allyl transfer that proceeds without the requirement of allylic organometallic reagents. This process, while not yet rendered catalytic in the metal (Ti or Mg), defines a unique and powerful convergent bond construction. Owing to the low cost of the metal-containing reagents, benign nature of the by-products (TiO_2 and magnesium (II) salts), and substrate-controlled stereoselection, this type of process in its current form should be of great utility in organic chemistry.

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[12] The empirical model described is based on the minimization of A-1,2 strain in a formal metallo-[3,3] rearrangement process, and does not account for the geometry at titanium. The proposed empirical model does not exclude a mechanism that follows from directed carbometalation and *syn* elimination. For a review of allylic strain as a principle for stereochemical control, see: R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841.

