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A Convergent Stereoselective Synthesis of Quinolizidines and Indolizidines: Chemoselective Coupling of 2-Hydroxymethyl-Substituted Allylic Silanes with Imines

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Substituted indolizidines and quinolizidines are heterocyclic motifs encountered in a range of bioactive natural products (Figure 1).[1] As such, these heterocycles have been the topic of considerable interest in organic and medicinal chemistry. Successful strategies for the assembly of substituted indolizidines and quinolizidines embrace a large swath of chemical reactivity spanning simple nucleophilic addition to cycloaddition, sigmatropic rearrangement, radical cyclization, C−H activation, iminium ion-based cyclization, and intramolecular reductive coupling.[2] The great wealth of strategies reported for accessing these bicyclic heterocycles reflects the level of interest from the chemical community and the challenges associated with the synthesis of these often highly substituted and stereodefined systems. Here we report a convergent stereoselective synthesis of substituted indolizidines and quinolizidines (**1**) through chemoselective coupling of functionalized allylsilanes with imines (**2** + **3**; Figure 2). This fragment union reaction, envisioned to proceed by chemoselective allyl transfer, was sought as a mechanism for delivering highly substituted and stereodefined allylsilanes (**4**).[3] Subsequent acid-promoted cationic annulation[4] was then anticipated to furnish substituted indolizidines and quinolizidines (**1**) in a stereoselective manner.[5,2i]

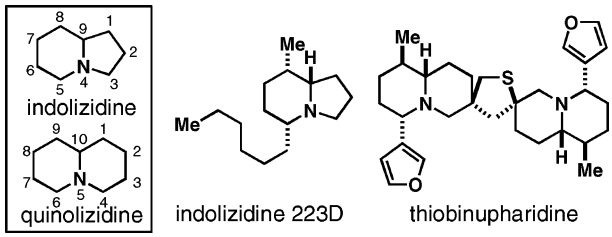


Figure 1. Introduction to indolizidines and quinolizidines.

While allylic silanes having the general structure **2** are useful for the synthesis of pyrans (via oxocarbenium ion chemistry[6]) and substituted five-membered rings (via metal-catalyzed TMM chemistry[7]), these substrates have not been described as allyl transfer reagents of the type required here (**2** + **3** → **4**). Nevertheless, we speculated that Ti-mediated chemoselective allyl transfer between hydroxymethyl-substituted allylsilanes **2** and imines **3** would have the potential to furnish homoallylic amines having the general structure **4**. Here allylation would proceed by a mechanism that engages the unique reactivity of allylic alchohols[8] in preference to the well-established allyl transfer chemistry associated with allylic silanes.[3] Overall, the desired chemoselective coupling would deliver a product in which the allylsilane moiety remains intact for subsequent heterocycle synthesis (**4** → **1**).

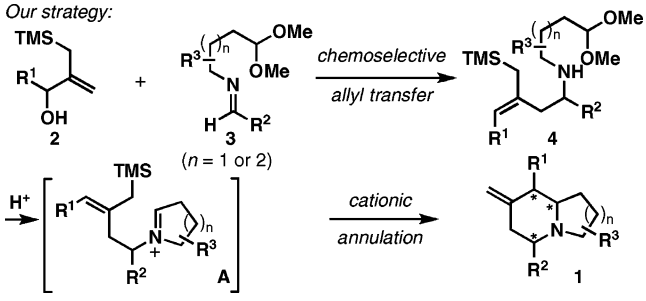
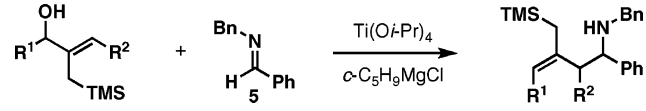
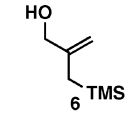
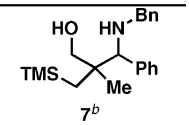
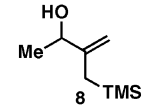
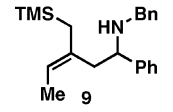
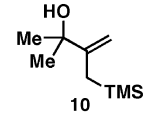
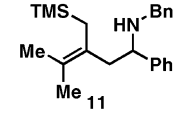
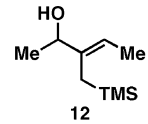
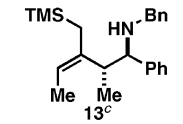


Figure 2. Indolizidine and quinolizidine synthesis via (top) chemoselective allyl transfer followed by (bottom) cationic annulation.

Our initial exploration of the required chemoselective coupling reaction is illustrated in Table 1. Overall, preformation of a Ti−imine complex (**5**, Ti(O*i*-Pr)$_4$, *c*-C$_5$H$_9$MgCl, Et$_2$O, −78 to rt)[9] followed by addition of a preformed lithium alkoxide of the allylic alcohol leads to successful C−C bond formation. Interestingly, substitution at the allylic position plays an important role in regioselection. Coupling of the simple allylic silane **6** with aromatic imine **5** provides a 1,3-amino alcohol as the major product. Here, C−C bond formation occurs at C2 of the allylic alcohol and delivers product **7** containing a quaternary center. With the secondary allyic alcohol **8**, very high levels of chemo- and stereoselectivity were observed in reductive cross-coupling with imine **5**. Here, allylsilane **9** is produced as a single isomer in 70% yield. As depicted in entry 3, this chemoselective coupling reaction is suitable for formation of allylsilanes **11** bearing tetrasubstituted alkenes. Finally, use of an allylic alcohol that contains a trisubstituted alkene

Table 1. Initial Exploration of the Chemoselective Coupling Reaction



entry	allylic silane	yield (%)	*E*:*Z*	dr	major product[a]
1	 **6**	75	–	–	 **7**[b]
2	 **8**	70	20:1	–	 **9**
3	 **10**	70	–	–	 **11**
4	 **12**	51	20:1	20:1	 **13**[c]

[a] Reaction conditions: **5** (1 equiv), Ti(O*i*-Pr)$_4$ (1.5 equiv), *c*-C$_5$H$_9$MgCl (3.0 equiv), allylic alkoxide (1.5 equiv), Et$_2$O, −78 °C to rt. [b] The desired homomoallylic amine product was isolated in 18% yield. [c] The relative stereochemistry of **13** was assigned by analogy to previous examples.[8]

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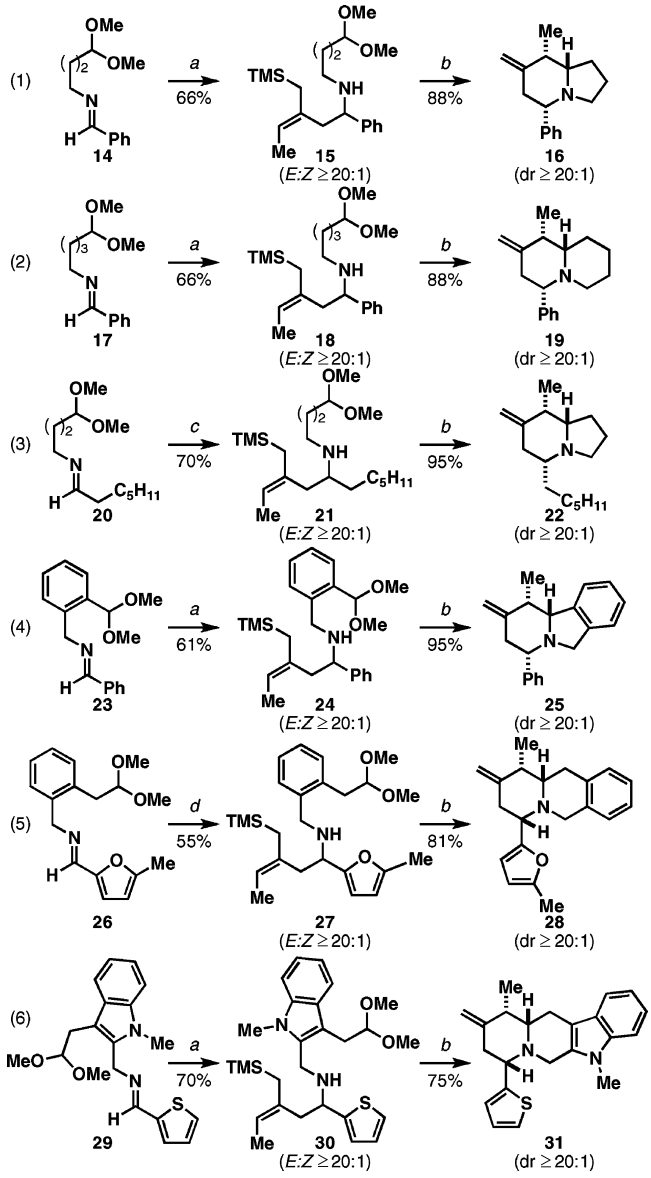

Figure 3. Synthesis of complex heterocycles. Reaction conditions: (*a*) Imine (1 equiv), Ti(O*i*-Pr)$_4$ (1.5 equiv), *c*-C_5H_9MgCl (3.0 equiv), **8** (1.5 equiv), Et_2O. (*b*) HCl(aq), THF. (*c*) Imine (2.0 equiv), Ti(O*i*-Pr)$_4$ (2.0 equiv), *n*-BuLi (4.0 equiv), **8** (1 equiv), Et_2O. (*d*) Imine (2.0 equiv), Ti(O*i*-Pr)$_4$ (3.0 equiv), *c*-C_5H_9MgCl (6.0 equiv), **8** (1 equiv), Et_2O.

was possible. As depicted in entry 4, titanium-mediated coupling of imine **5** with allylic alcohol **12** provides stereodefined allylic silane **13** with very high levels of stereoselectivity.

With a method for chemoselective allyl transfer in hand, we initiated studies aimed at application of this transformation to the synthesis of complex indolizidine and quinolizidine systems (**4** → **1**). To accomplish this, our investigations began with the study of the simple aromatic imine **14** (eq 1 in Figure 3). Gratifyingly, the reductive cross-coupling reaction with **8** defines an effective means of preparing the stereodefined acetal-containing allylsilane **15** (66%; *E*/*Z* ≥ 20:1). Acid-promoted cyclization then proceeds in good yield, delivering the stereodefined trisubstituted indolizidine **16** (88%, dr ≥20:1). As depicted in eq 2 in Figure 3, use of imine **17** in this two-step annulation process provides a similarly facile and stereoselective pathway to trisubstituted quinolizidine **19**.

With the application of a recently described procedure for the coupling of aliphatic imines with allylic alcohols,[10] this convergent heterocycle-forming process can be used to prepare systems containing all-alkyl substitution (eq 3 in Figure 3). Again, indolizidine formation occurs in high yield (95%) with superb stereoselection (dr ≥20:1) and furnishes 7-exomethylene indolizidine 223D (**22**).[11]

Delighted that this synthetic strategy proved successful for the synthesis of simple indolizidine and quinolizidine architectures (**16**, **19**, and **22**), we questioned whether this process would be useful for the synthesis of more complex polycyclic systems. As depicted in eqs 4−6 in Figure 3, use of substrates containing additional functionality between the imine and acetal leads to the formation of complex stereodefined polycyclic heterocycles in a concise and stereoselective fashion.

In conclusion, we have defined a new convergent bond construction that serves as a powerful foundation for heterocycle synthesis. A unique chemoselective functionalization of hydroxymethyl-substituted allylic silanes provides a facile and stereoselective entry to the indolizidine and quinolizidine cores. In addition to highlighting the utility of this heterocycle preparation in the synthesis of 7-exomethylene indolizidine 223D, we have demonstrated the basic coupling process for the assembly of complex polycyclic heterocycles containing furans, thiophenes, and indoles. While the control of absolute stereochemistry in this annulation remains a challenge, the present contribution defines a reaction sequence of broad utility for heterocycle synthesis. Because of (1) the ubiquitous nature of indolizidines and quinolizidines in natural products and small molecules of biomedical relevance, (2) the ready availability of the coupling partners, (3) the functional-group compatibility of the chemoselective allyl transfer reaction, (4) the stereoselectivity of the cationic annulation, and (5) the inexpensive nature of the reductive cross-coupling process, we look forward to future developments that emerge from these initial findings.

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Supporting Information Available: Experimental procedures and tabulated spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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