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Synthesis of Secondary Amines by Titanium-Mediated Transfer of Alkenyl Groups from Alcohols

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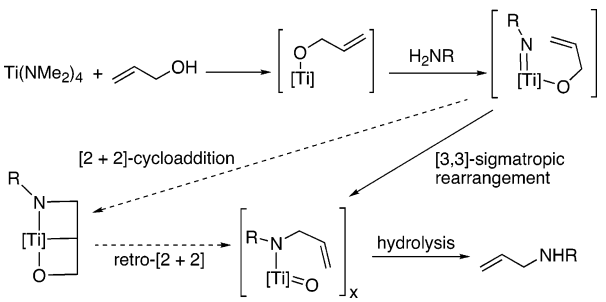
Allylic amines are found in some natural products and are of great synthetic utility.[1] Methods for the selective synthesis of various allylic amines are generally marked with several challenges, among which are preventing overalkylation if a secondary amine is desirable and control of the regioselectivity of the allylic substituent.[2] A method for the direct use of allylic alcohols, perhaps the most abundant source of commercially available allylic groups, as the allylating agent is preferable. Here, we describe an initial study on the use of commercially available $Ti(NMe_2)_4$ as the mediator for selective conversion of primary amines to secondary allylic amines, potential mechanisms, and a remarkable increase in scope for the reaction.

The design for the synthesis is shown in Scheme 1.[3] $Ti(NMe_2)_4$ has been used for in situ generation of titanium imido complexes for the hydroamination of alkynes and alkenes.[4] In this work, primary amine is added to in situ generated $Ti(NMe_2)_3(OR)$ to access an imido alkoxide. Three diverse amines were chosen to explore the reaction scope: aniline, cyclohexylamine, and benzhydrylamine.[5] These amines were reacted with methyl- and phenyl-substituted allylic alcohols in addition to parent allyl alcohol (Table 1).[6] The reactions are selective for allylic transposition.[7] To further probe the regioselectivity, we prepared 1,1-dideuteroallyl alcohol (Scheme 2).[8,9] A single product is observed by ^1H and ^2H NMR.

Lack of reactivity was noted with some allylic alcohols under these conditions (Chart 1). No reactivity was seen with $Me_2C{=}CHCH_2$-OH and any of the amines employed, which is readily explained by steric considerations. More puzzling was the lack of reactivity with 2-methylallyl alcohol. Adding a methyl group to this position should not inhibit a [3,3]-sigmatropic rearrangement (Scheme 1).

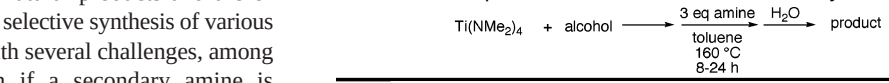
Scheme 1. Conceptual Scheme for the Use of Allylic Alcohols in the Allylation of Primary Amines. Other Ligands on Titanium Not Shown

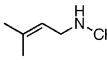
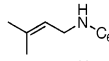
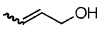
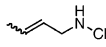
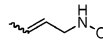
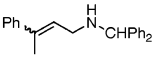
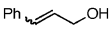
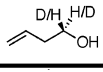
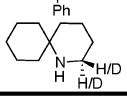


Rearrangement of imido allylic alkoxides has been studied as a possible step of the SOHIO process for acrylonitrile synthesis.[9,10] The mechanism proposed for these processes is a [3,3]-sigmatropic rearrangement to generate the allylic amido and a terminal oxo. In academic[11] and industrial[12] allylic alcohol rearrangements, a similar mechanism is postulated.[13] Inhibition by methylation of the 2-position of allyl alcohol brought this mechanism into question for this titanium system. An alternative is a [2 + 2]/retro-[2 + 2] pathway (Scheme 1), which appears to have received little attention in the literature. There is ample precedent for the inhibition of [2 + 2]-cycloadditions on olefin substitution,[14] and this pathway offers an explanation for 2-methylallyl alcohol inactivity.

Unlike a methyl group in the 2-position, 2-phenylallyl alcohol did show activity with some amines (entries 13 and 14, Table 1). This increased activity with phenyl suggests that the inhibition by a 2-methyl group has an electronic component. On formation of

Table 1. Examples of Titanium-Mediated Amine Allylation



	amine[a]	alcohol	product	GC (isolated) yield
1	$PhNH_2$			78 (51)
2	Ph_2CHNH_2			72 (50)
3	$CyNH_2$			63 (30)
4	$PhNH_2$			(74)
5	Ph_2CHNH_2			(72)
6	$CyNH_2$			(69)
7	$PhNH_2$			57 (31)
8	$PhNH_2$			(80)[b]
9	Ph_2CHNH_2			87[c,d]
10	$CyNH_2$			61 (30)[c]
11	$PhNH_2$			69 (57)[c]
12	Ph_2CHNH_2			68 (54)[e]
13	$PhNH_2$			40 (31)
14	$CyNH_2$			58 (45)
15	$PhNH_2$			37 (20)
16	$CyNH_2$			63 (35)[f]

[a] Cy = C_6H_{11} (cyclohexyl). [b] Ratio of *cis*:*trans* 1:2. [c] Ratio of *cis*:*trans* 2:1. [d] Estimated GC/FID yield. Chromatography did not completely separate product from starting amine. [e] Ratio of *cis*:*trans* 1:5. [f] Yields for protio.

Scheme 2. Reaction with Deuterated Allyl Alcohol

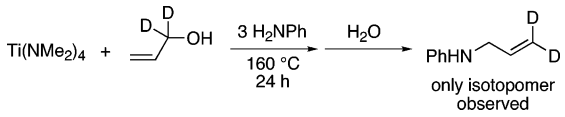


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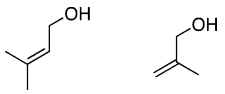
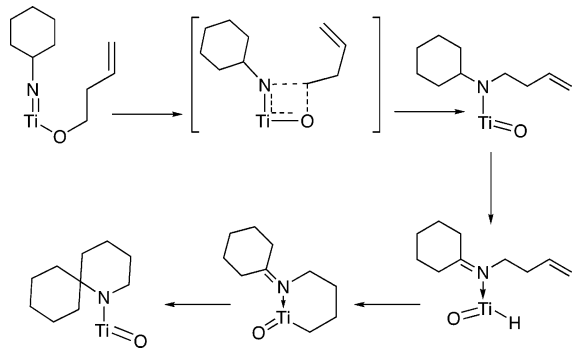
Chart 1. Olefin-Substituted Allylic Alcohols with Olefin Substitution Patterns that Inhibited Reactions



Scheme 3. Possible Mechanism for the Homoallylic Group Transfer and Cyclization. Likely Oligomerization of Terminal Oxo Complexes and Other Ligands Are Not Shown for Simplicity



the Ti−C bond in the bicyclic intermediate (Scheme 1), a partial negative charge will be present at the 2-carbon of the allyl. Addition of a phenyl group should resonance stabilize this charge.

An attempted reaction with homoallylic alcohol and cyclohexylamine shows that this substrate also transfers the alkyl group![15] Interestingly, the olefinic amine is not the final product. A cyclization occurs with the apparent insertion of the olefin into the methine hydrogen of the cyclohexyl group. The final product is the spiro compound shown in Table 1.

The 1-aza-spiro[5.5]undecane core is found in several natural products, such as histrionicotoxin.[16] The parent spiro compound has been synthesized previously in six steps in ∼6% overall yield.[17]

For a deuterium labeling experiment, the homoallylic alcohol with two deuteriums on the hydroxyl-bearing carbon was synthesized.[18] Contrary to allyl, the carbon bearing the label ends the reaction attached to nitrogen in the spiro product (Table 1).

The labeling experiment suggests a new mechanism for the nitrogen alkylation step. The C−N bond forming step may involve migration of the alkyl from the alkoxide to an imido or amido ligand (Scheme 3). The alkyl transfer step is unusual but reminiscent of the four-center mechanism found in reaction of zirconium alkyls with Br_2.[19] In addition, the mechanism proposed here is similar to that observed in Re oxo hydroxides by Mayer and co-workers, where hydrogen transfer occurs in a unimolecular migration.[20] The exact mechanism is still under investigation.

The chemistry illustrated provides a simple, effective route to selectively produce secondary allylic amines in a regioselective manner. The starting materials are readily available alkenyl alcohols, allylic or homoallylic. Currently, we favor the [2 + 2]-pathway (Scheme 1) for this titanium system due to 2-methyl inhibition in allyl transfer.[21] While other methodologies exist for amine allylation,[2] the flexibility of these mechanisms potentially opens new avenues useful for organic synthesis.

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Supporting Information Available: Synthetic details and characterization data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) All the combinations were attempted with the alcohols listed with all three amines. "Missing" reactions in Table 1 did not result in product by GC in initial screens with this mediator.
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