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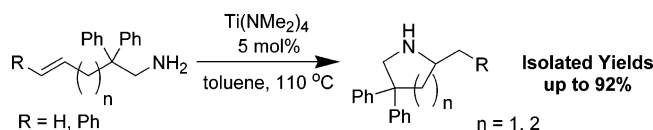
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Received February 23, 2005

ABSTRACT



Commercially available $\text{Ti}(\text{NMe}_2)_4$ has been used effectively as a precatalyst in a facile protocol for the intramolecular hydroamination of aminoalkenes to yield pyrrolidine and piperidine heterocyclic products with isolated yields up to 92%. Geminally substituted substrates display the highest reactivity. This precatalyst is also effective for the hydroamination of activated internal alkenes, providing access to more complex heterocyclic target molecules.

The catalytic addition of N–H across a carbon–carbon multiple bond (hydroamination) is an intense area of investigation with many recent results highlighting the hydroamination of alkynes to yield enamine and imine products.¹ This synthetic transformation is desirable due to the highly atom-economic synthesis of imines from readily available starting materials, and the extension of these efforts toward the hydroamination of alkenes continues to be an important area of research.² To this end, Marks and co-workers have pioneered the area of olefin hydroamination with a wide range of highly active lanthanide catalysts that are effective for intramolecular versions of this transformation³ as well as select intermolecular versions.⁴ Our research

group and others have furthered these efforts in lanthanide and group 3 catalyzed olefin hydroaminations to include noncyclopentadienyl complexes that display desirable reactivity trends.⁵ Unfortunately, all of the aforementioned group 3 and lanthanide catalysts display limited functional group tolerance and high moisture sensitivity, making their routine preparation and application in synthesis problematic.

In an effort to develop catalytic systems that are more robust, functional group compatible, and easily handled, late transition metal catalysts are being developed to mediate both the intermolecular alkene hydroamination reaction^{2d,6} and, more recently, the intramolecular hydroamination of ami-

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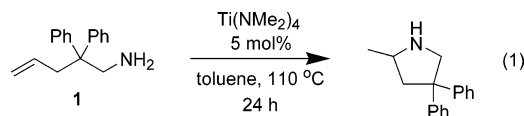
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noalkenes.⁷ However, the intermolecular reactions are largely limited to activated terminal olefins, such as vinylarenes and dienes,^{2d} alkenes substituted with electron-withdrawing groups,^{6c} or highly strained alkenes, such as norbornene.⁸ While significant progress has been made in this area, the hydroamination of alkenes remains an important synthetic challenge with no generally applicable catalysts having been reported.

Hydroamination catalysis with group 4 transition metals is an area of intense investigation.⁹ The hydroamination of alkynes using these catalyst systems is well established with several systems having been developed for the regioselective hydroamination of both internal and terminal alkynes with a wide range of substrates.^{9b,e,m,10} Notably, the application of commercially available $\text{Ti}(\text{NMe}_2)_4$ for both the intra- and intermolecular hydroamination of alkynes and allenes has been reported.¹¹ However, the hydroamination of alkenes using titanium remains a significant challenge with the only reported examples of early transition metals being used for this transformation requiring the highly strained norbornene olefin with select aniline derivatives.¹² Alternatively, more reactive group 4 cationic catalysts, which are isoelectronic to known group 3 systems, have been shown to carry out intramolecular alkene hydroamination with secondary amines exclusively.¹³ Once again, these cationic complexes are plagued with extreme moisture sensitivity and furthermore, they are ineffective for the hydroamination of alkenes with primary amines. Herein we report the first examples of titanium-catalyzed hydroamination of unactivated alkenes in an intramolecular fashion to yield pyrrolidines and piperidines (eq 1) in excellent yields. Most importantly, *these reactions are mediated by the commercially available titanium precatalyst, $\text{Ti}(\text{NMe}_2)_4$, in a facile protocol that*

utilizes simple syringe techniques to deliver a modest catalyst loading of 5 mol % to solutions of aminoalkene substrates.



Initial experiments focused on the intramolecular hydroamination of the easily prepared 2,2-diphenyl-4-penten-1-amine (**1**) substrate (eq 1).^{5b} The catalytic reaction was performed in toluene at 110 °C with a 5 mol % precatalyst loading for 24 h. By using ^1H NMR spectroscopy, the characteristic disappearance of two olefin signals centered at δ 5.44 and 4.95 ppm and the appearance of two new proton signals at δ 2.38 and 1.80 ppm were used to measure the progress of the reaction. On an NMR tube scale, it was noted that the reaction had proceeded to completion within 1 h at 110 °C. We wondered if the highly elevated temperatures were required, and thus, we also performed this reaction at reduced temperatures, such as 70 and 45 °C. At these lower temperatures, within 2.5 h, the desired products were observed to form in 70% and 38% conversion, respectively, and no appreciable reaction was seen at room temperature in this period of time. However, unidentified alkene-containing side products (as indicated by the appearance of new olefinic peaks in the ^1H NMR spectrum) were also formed, and prolonged reaction times did not result in the clean product formation that had been observed in the 110 °C experiment. Consequently, the higher temperature protocol was employed for all subsequent investigations.

To verify that this precatalyst is amenable to the milligram-scale preparation of this class of desirable heterocyclic products, the reaction shown in eq 1 was performed using 131 mg (0.55 mmol) of the starting material. The requisite aminoalkene **1** was purified by distillation from CaH_2 . In the other cases reported here, amines were purified by distillation and dried over 4 Å molecular sieves for approximately 24 h before use. Under inert atmosphere, a solution of **1** was prepared in approximately 2 mL of toluene before loading 9.0 μL of commercially available $\text{Ti}(\text{NET}_2)_4$ precatalyst by microsyringe. (It should be noted that $\text{Ti}(\text{NMe}_2)_4$ and $\text{Ti}(\text{NET}_2)_4$ can be used interchangeably for these reactions.) The reaction mixture was heated to 110 °C for 24 h and quenched with CH_2Cl_2 , and then all volatiles were removed in vacuo to give a brown oily solid that could be purified by column chromatography and isolated in 92% yield (Table 1, entry 1). With both catalytic activity and ease of synthetic protocol established for $\text{Ti}(\text{NR}_2)_4$ as a precatalyst, preliminary investigations of the scope of the reaction were undertaken.

In Table 1, the dramatic Thorpe–Ingold effect on the intramolecular hydroamination, as mediated by this catalyst, is apparent. Only the geminally substituted substrates undergo intramolecular hydroamination within 24 h (entries 1–3), and as the steric bulk of the substituent is reduced, the efficiency of this reaction is also reduced (entry 1 compared with entry 3). In the case of the 2,2-dimethyl-4-penten-1-amine substrate (entry 3) it should be noted that the volatility

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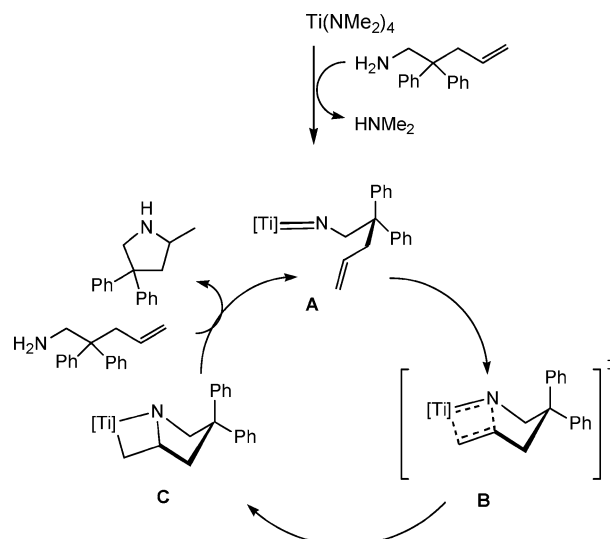
Table 1. Scope of Reactivity with $\text{Ti}(\text{NMe}_2)_4$ as a Precatalyst

Entry	aminoalkene	product	time [h]	yield [%]
1			24	92 ^a
2			24	80 ^a
3			24 96 120	32 ^b 52 ^b 43 ^c
4		 + 	168	26 ^c 4a:4b 1.4:1
5			96	38 ^b
6		 + 	24	52 ^c 6a:6b 1.4:1 ^d
7			24	—

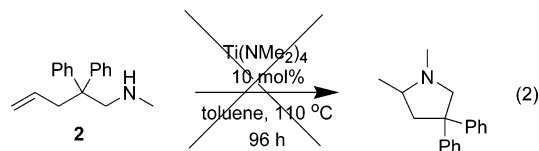
^a Isolated yield. ^b Yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. ^c Isolated yield following derivatization using benzoyl chloride. ^d Ratio determined by GCMS.

of the resultant product required its derivatization with benzoyl chloride to obtain an isolated yield. Both five-membered (entry 1) and six-membered (entry 2) heterocyclic products can be prepared using this precatalyst in very good isolated yields. It should be noted that by ^1H NMR spectroscopy these reactions were observed to proceed to >98% conversion. However, the comparable seven-membered ring could not be prepared, even when the appropriate geminally substituted substrate and extended reaction times (up to 240 h) were used. With only a single substituent on the ring, the reaction times need to be extended up to 170 h to obtain even modest yields. However, in the absence of substituents on the substrate, no intramolecular hydroamination activity is observed, regardless of reaction times and reaction temperatures up to 140 °C in xylenes-*d*₁₀ (entry 7).

The dramatic effect of geminally substituted substrates is consistent with a chairlike transition state (**B**, Figure 1) that has been proposed as the transition state for intramolecular hydroamination reactions.^{3b,5a} However, what was not clear from these experiments was the nature of the reactive Ti–N bond in the catalytically reactive species (**A**, Figure 1). Bergman, Doye, Odom, Mountford, and work in our laboratories have shown that for the catalytic hydroamination of alkynes **A** is a titanium imido species.^{9d,k,14} However, the

**Figure 1.** Proposed mechanism for titanium catalysis of olefin hydroamination.

possibility of olefin insertion into a Ti–N σ -bond, as has been established in the case of group 3, lanthanide, and cationic group 4 mediated intramolecular olefin hydroamination, could not be ruled out with the aforementioned experiments.^{4b,5a,13} Consequently, the related substrate containing a secondary amine was prepared (**2**) and was tested for olefin hydroamination activity with $\text{Ti}(\text{NMe}_2)_4$ precatalyst (eq 2). Elevated reaction temperatures and prolonged reaction times did not result in the formation of the desired *N*-substituted pyrrolidine product. Our observations support the proposal that catalysis is proceeding via the in situ preparation of a titanium imido species, consistent with the better-understood alkyne hydroamination examples reported in the literature. However, rigorous isolation, characterization, and comparative reactivity studies of related titanium imido complexes is an area of current research focus.

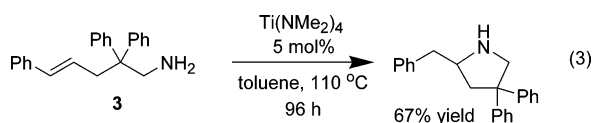


The proposed chairlike transition state and dramatic impact of steric effects upon the observed rates of reaction suggest that diastereoselectivity could be achieved in the cases of entries 4–6. Indeed, modest diastereoselectivities were observed in the case of monosubstituted substrates (entries 4 and 5). Interestingly, when two different substituents of more similar steric demands (Ph and Me) were incorporated into the geminally substituted substrate (entry 6), comparable

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diastereoselectivity to the Ph, H substituted example (entry 4) was observed. For entries 4 and 6, the major diastereomer was isolated by column chromatography, and selective NOE NMR spectroscopic experiments confirmed that the syn products were preferred over the anti products. The observed diastereoselectivity is consistent with the chairlike transition state and the equatorial location of the larger of the two substituents.¹⁵ Due to the elevated temperatures required to promote the desired reactivity and the distal location of the stereo-differentiating substituents, the poor diastereoselectivity observed in this reaction is not surprising and is consistent with previous reports of diastereoselectivity for the intramolecular hydroamination of substrates with substituents in the 2 position.¹⁶

To further probe the substrate tolerance of the $\text{Ti}(\text{NMe}_2)_4$ precatalyst, we investigated its use for the hydroamination of internal alkenes. In particular, substrate **3** was prepared and tested for intramolecular hydroamination (eq 3).



A prolonged reaction time of 4 days (96 h) was required to obtain the desired product with an isolated yield of 67% (77% conversion as observed by ^1H NMR spectroscopy). However, further investigations into the application of internal alkenes

(15) Based on the relative *A* values for Ph and Me substituents; see: Allinger, N. L.; Freiberg, L. A. *J. Org. Chem.* **1966**, *31*, 804. Eliel, E. L.; Manoharan, M. *J. Org. Chem.* **1981**, *46*, 1959.

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revealed that an activated olefin, such as the styrene derivative shown in **3**, is required and bis-alkyl substituted olefins remained inert to the catalytic conditions described above.

In summary, we have established that commercially available $\text{Ti}(\text{NMe}_2)_4$ may be used in a facile protocol for the catalytic preparation of pyrrolidine and piperidine heterocyclic products from aminoalkene substrates in good yields. This reaction is particularly efficient for geminally substituted substrates and proceeds with predictable, although modest, diastereoselectivity due to the chairlike transition state of the intramolecular hydroamination reaction. Substrate screening provided qualitative results consistent with a catalytic mechanism invoking the in situ preparation of a catalytically active titanium imido species, and more detailed mechanistic investigations are underway. Most importantly, this simple precatalyst is effective for the intramolecular hydroamination of not only terminal alkenes, but also activated internal alkenes. These preliminary results encourage the development of new, neutral, titanium catalysts for the hydroamination of alkenes and current efforts focus on the development of chiral titanium catalysts for the enantioselective synthesis of N-containing heterocycles.

Acknowledgment. We thank the Natural Science and Engineering Research Council of Canada (NSERC), Boehringer Ingelheim Canada Ltd., and the University of British Columbia for financial support of this work.

Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL0503992