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Catalytic Intermolecular Hydroamination of Methylenecyclopropanes

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*Summary: The octahedral titanium catalyst Ti(Ph$_2$PNpy)$_2$(NEt$_2$)$_2$ (**1**) was found to be an efficient catalyst for the hydroamination of methylenecyclopropane with either aromatic or aliphatic amines. For a symmetrical methylenecyclopropane, only one product is obtained in high yield. The reaction of complex **1** with ethylamine and aniline produces the dimeric titanium complexes Ti$_2$(Ph$_2$PNpy)$_2$(μ-NEt)$_2$ and Ti$_2$(Ph$_2$PNpy)$_2$(μ-NPh)$_2$, respectively.*

Addition of a nitrogen−hydrogen bond over an unsaturated carbon−carbon bond is a highly desirable transformation in organic chemistry, offering an efficient synthetic route to amines, enamines, and imines. Amines especially play an outstanding role as products and intermediates in the chemical industry.[1] However, such a transformation of unsaturated hydrocarbons does not occur spontaneously in the presence of amines. Catalytic hydroamination offers a very convenient solution for lowering the activation barrier for those reactions. An efficient hydroamination process can offer significant economical and environmental benefits compared to classic methods for the synthesis of the same target compounds. Over the years, a great deal of effort went into finding the most efficient catalysts that will promote this process. Among the different catalysts for the hydroamination reaction, group IV metal complexes[2,3] have provoked widespread interest, due to their general reactivity and ubiquitous availability compared to toxic metals (Hg, Tl,[4] U, and Th[5]), or more expensive lanthanides[6] and late-transition-metal complexes (Ru,

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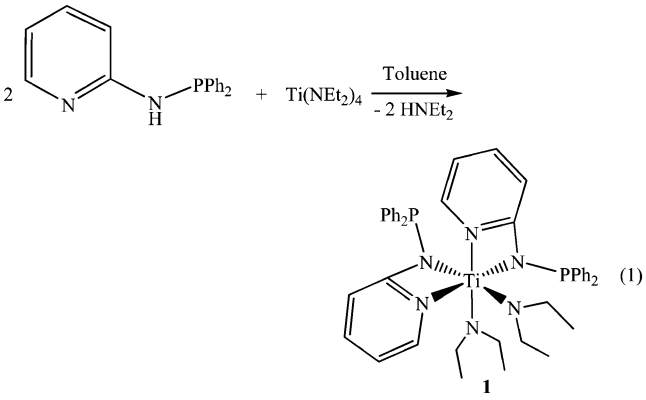
Pd, Rh, Pt, and Ag).[7] However, to date, the field of intermolecular hydroamination reactions catalyzed by group IV metal complexes remained limited to alkyne, allene, and norbornene substrates.[2] Therefore, one of the main challenges in this field is with regard to the expansion of the reaction scope.

Here we introduce a new titanium catalyst that promotes the intermolecular hydroamination of a new class of substrates, the methylenecyclopropanes (MCPs), with aliphatic and aromatic amines. MCPs have been tested in hydroamination reactions promoted by late transition metals[8] and lanthanides,[9] producing allylamines and imines correspondingly.

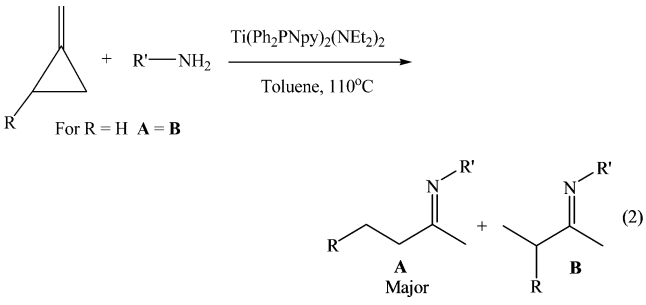
The octahedral titanium catalyst $Ti(Ph_2PNpy)_2(NEt_2)_2$ (**1**) was synthesized in a one-step reaction between 2 equiv of the neutral ligand 2-((diphenylphosphanyl)-amino)pyridine and 1 equiv of the homoleptic tetrakis-(diethylamino)titanium (eq 1). The structure of **1** and



(1)

the dynamic behavior of the chelating ligands responsible for the formation of elastomeric polypropylene when complex **1** was activated with MAO (methylalumoxane) have been recently determined.[10]

The scope and chemo- and regioselectivity of the intermolecular hydroamination of unsymmetrical and symmetrical MCPs promoted by complex **1** are summarized in eq 2 and Table 1. On the basis of the studied



(2)

mechanisms for the hydroamination of alkynes promoted by titanium complexes,[3a,b] a plausible mechanism for the intermolecular hydroamination of MCP's with amines is presented in Scheme 1. In the first step of the mechanism, complex **1** reacts with primary amines, yielding complex **2**, which eliminates an amine to produce the active imido complex **3**. This complex exists in equilibrium with its dimer form (**4** and **5**). We suggest

Table 1. MCPs Hydroamination Results with 1 as a Precatalyst

entry	R	R′	% cat.[a]	time (h)	**A** (%)	**B** (%)	conversn (%)	isolated yield **A** (**B**)[b]	N_t[c] (h^{-1})
1	Ph	Et	5	4	100	0	38.5		1.93
2	Ph	Et	5	40	100	0	100	95	0.50
3	Ph	Ph	5	4	87	13	73		3.65
4	Ph	Ph	5	17	87	13	100	83 (10)	1.15
5	Ph	Bu	5	20	100	0	94	90	6.25
6	Ph	^{i}Pr	5	96	84	16	80	63 (8)	0.41
7	Ph	(*o*-^{i}Pr)$_2$Ph	5	120	100	0	24		0.04
8	Ph	(*o*-^{i}Pr)$_2$Ph	5	2.5[d]	100	0	100	97	0.01
9	H	Ph	2	36	100	*e*	78		1.08
10	H	Ph	2	45	100	*e*	95	90	1.05
11	H	Et	2	36	100	*e*	93	90	1.29
12	H	Bu	2	36	100	*e*	60	56	0.83
13	H	^{i}Pr	2	36	100	*e*	81	76	1.12

[a] All of the hydroamination reactions were performed in toluene-d_8 as a solvent at 110 °C. [b] Percent yield of the isolated products. [c] Turnover frequencies ($n_{product}/(n_{cat}$ h)) measured in toluene-d_8. [d] Reaction time in months. [e] R = H; therefore, **A** = **B**.

that 1,2-insertion of the MCP double bond into the Ti=N bond results in the formation of the azatitanacyclobutane complex **6**.[11,12] Complex **6** may undergo two different ring-opening transformations to form more stable five-membered-ring complexes (**7A** and **7B**). The cleavage of the C_2-C_3 bond (pathway *a*) will result in the formation of **7A**, whereas the cleavage of the C_2-C_4 bond (pathway *b*) will induce the formation of complex **7B**. Complex **7A** is more stable than **7B**, since the metal in the former complex is bonded to a benzylic carbon, whereas in the latter complex the metal is bonded to a primary carbon. Therefore, pathway *a* is expected to be the preferential route, as observed from the product distribution in Table 1. Protonolysis of complexes **7A** and **7B** will form the corresponding bis(amido) complexes (**8A** and **8B**). As in the hydroamination of alkynes, we suggest that the concomitant α-elimination of the enamines will regenerate the imido complex **3**. Products **A** and **B** will most likely be obtained by the tautomerization of **9A** and **9B**, correspondingly.

In the intermolecular hydroamination of unsymmetrical MCPs with aliphatic amines, a slightly de-

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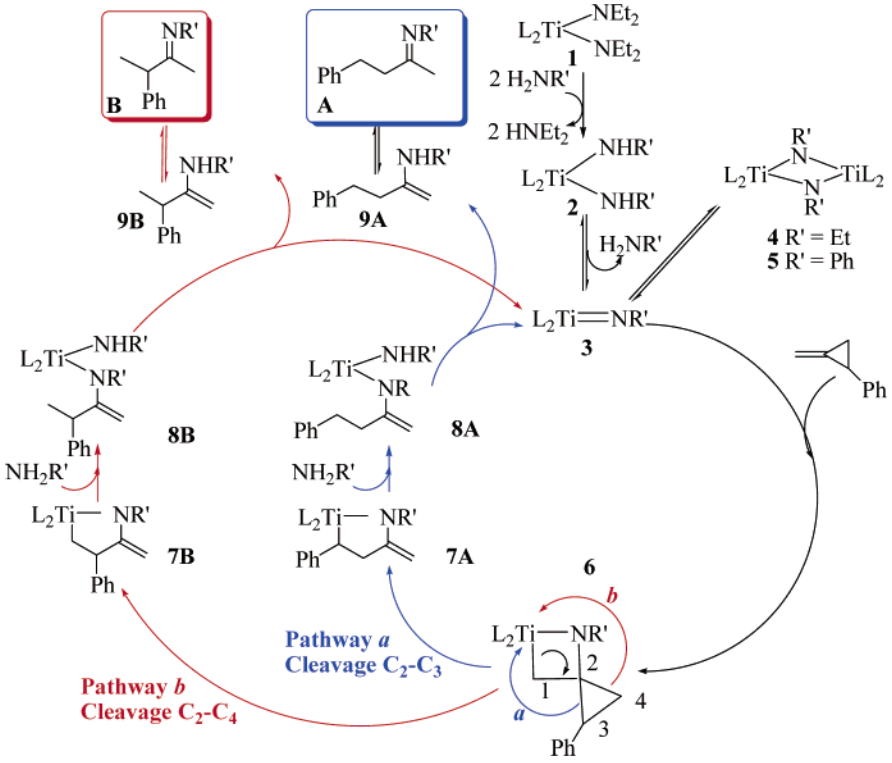
(12) As followed by NMR, the reaction of 1 equiv of complex **1** with 2 equiv of aniline and 1 equiv of PhMCP shows after heating (110 °C) for a short amount of time the disappearance of the signal (5.50 ppm, doublet of quartets) associated with the exocyclic methylene group of the PhMCP, and the appearance of new signals (5.446 and 5.455 ppm, two doublets with $^2J_{HH} = 4.5$ Hz) associated with the $-CH_2-$ group of the azatitanacyclobutane **6**.

Scheme 1. Proposed Catalytic Cycle for the Intermolecular Hydroamination of MCPs



creased trend in turnover frequencies (N_t) is observed as compared to the aromatic amine (entries 2, 4, and 6 in addition to entry 5). This result may reflect the increased nucleophilicity of the aliphatic amines, promoting the formation of the bis(amido) species (**2**) out of the catalytic cycle (Scheme 1). In comparison to organolanthanide complexes, the opposite effect was observed for similar substrates.[9] However, the hydroamination of an ortho-substituted amine (entries 7 and 8) is extremely slow due to the steric hindrance between the ortho substituent and the diphenylphosphino motif of the ligands, precluding the formation of the active imido complex **3**. With regard to the regioselectivity, one or two regioisomers are observed (**A** and **B**, eq 2). It is most likely that both isomers are products via a 1,2-addition of the Ti=N into the MCP exo methylene. For the metallacyclic complex **6** two regioisomers can be expected (**6a** and **6b**).[11] Complex **6a** will be the preferred isomer, due to the lack of steric hindrance between the amine substituent (R′) and the diphenylphosphine

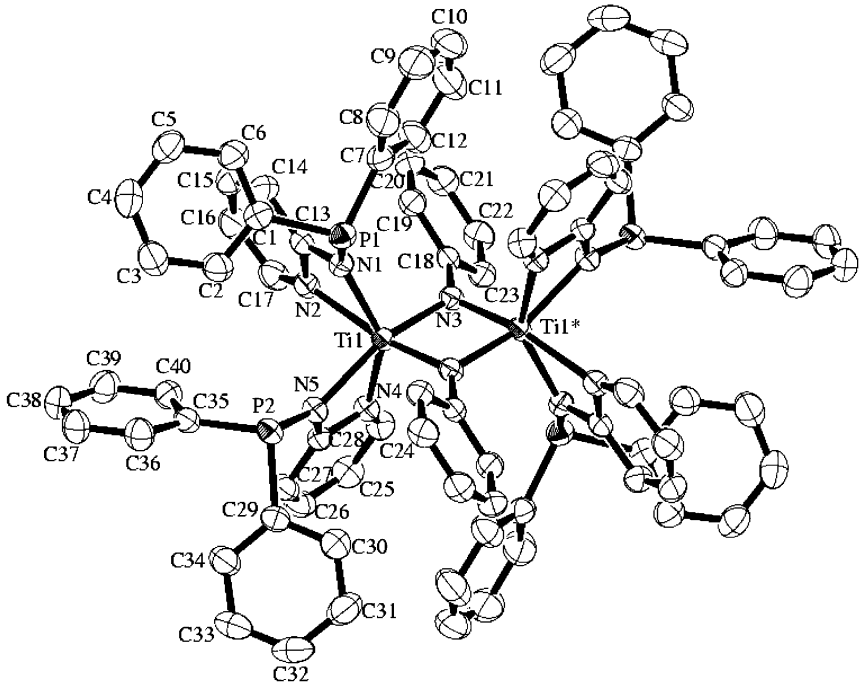
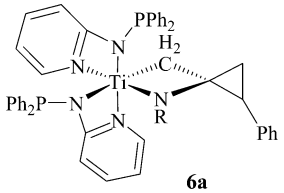
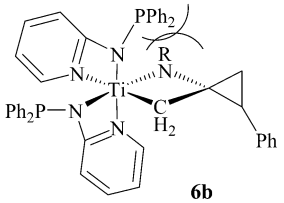


Figure 1. ORTEP plot of the structure of complex $Ti_2(Ph_2PNpy)_4(\mu\text{-}NPh)_2$ (**5**). Thermal ellipsoids are given at the 50% probability level.



6a



6b

moiety. In addition, the latter group ($-PPh_2$) will always be expected to be transoid to the phenyl group of the PhMCP.[12]

In all cases the linear imine **A** is observed as the major product. For the less bulky amine, the reaction is also chemoselective, producing 100% of the linear imine **A**. The selectivity results are comparable to those obtained for MCP hydroamination promoted by organlanthanides.[9]

In the case of the symmetrical MCP, only one product is expected (R = H in eq 2). In general, the PhMCP reacts faster than the MCP (except in the reaction with $^{i}PrNH_2$); however, the hydroaminations of MCP with different types of amines (entries, 10, 11, and 13) produce similar N_t values.

To shed some light on the fate of the precatalyst in the hydroamination process, the reactivity of complex **1** with various primary amines was studied. The reaction of complex **1** with an excess of ethylamine or aniline produces rapidly the dimeric titanium complexes $Ti_2(Ph_2PNpy)_2(\mu\text{-}NEt)_2$ (**4**)[10a] and $Ti_2(Ph_2PNpy)_2(\mu\text{-}NPh)_2$ (**5**), respectively. The ORTEP plot of complex **5** is shown in Figure 1.

In complex **5** both titanium atoms exhibit an octahedral environment, with N1 and N4 disposed in apical positions. The four-membered ring Ti−N(3)−Ti−N(3)* is totally planar (sum of internal angles 360.0°), although both bridging nitrogens are placed asymmetrically (Ti(1)−N(3) = 2.0117(14) Å; Ti(1)−N(3)$^{\#}$ = 1.8794(14) Å). Complex **4** was found to be isostructural with complex **5**.[10a]

In conclusion, although MCPs are highly strained compounds, they are remarkably stable. These properties make them suitable as substrates for the hydroamination reaction. We have shown here a new catalyst that can promote MCPs hydroamination reaction in high isolated yields and good stereoselectivity.

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Supporting Information Available: Text, tables, and figures giving details of the syntheses and NMR analyses of compounds **A**, **B**, and **5**, a representative diagram for the formation of imine as a function of time, and the crystallographic data for the crystal structure of complex **5**; crystallographic data are also available as a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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