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Selective C−H Activation α to Primary Amines. Bridging Metallaaziridines for Catalytic, Intramolecular α-Alkylation

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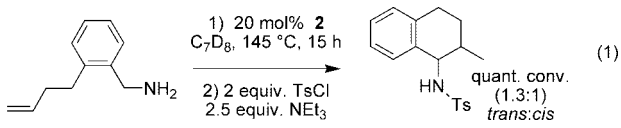
New catalytic approaches for the synthesis of α-substituted amines provide efficient routes to many products for the pharmaceutical, agrochemical, and fine chemical industries. One catalytic method, hydroamination, continues to be intensely investigated for the intra- and intermolecular addition of N−H bonds of amines across alkenes.[1] Recently, Hartwig disclosed the first efficient example of catalytic intermolecular α-functionalization of secondary amines with alkenes (the hydroaminoalkylation reaction) to give α-alkylated secondary amine products.[2] Here we demonstrate that easily prepared primary aminoalkenes can be used as substrates for intramolecular α-functionalization to generate amine substituted cycloalkanes (eq 1). Importantly, this approach allows for protection group free alkylation α to nitrogen, giving primary amines ready for further synthetic manipulation.

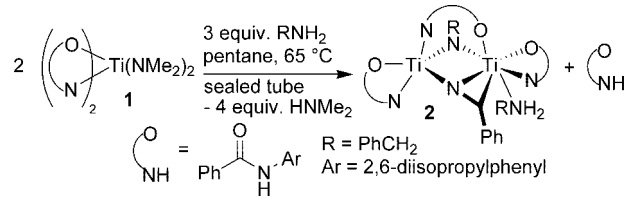


(1)

In 2001, Doye noted that intermolecular hydroamination reactions attempted with (*S*)-1-phenylethylamine resulted in the partial racemization of this α-substituted amine,[3] via a postulated α-C−H activation reaction. More recently, his group reported that aminoalkenes in combination with some Ti hydroamination catalysts undergo α-alkylation to give modest quantities of amino substituted cycloalkane byproduct.[4] Once again, an α-C−H activated reactive intermediate has been proposed. This is similar to Hartwig's hydroaminoalkylation reaction, where secondary amines are proposed to undergo an α-C−H activation reaction to give Ta η^2-imine (metallaaziridine) reactive complexes.[5] These η^2-imine species have not been observed but are proposed in analogy to extensively investigated Zr η^2-imine complexes (zirconaaziridines),[6] which have been used in the stoichiometric preparation of a broad range of α-alkylated secondary amine products upon workup.[7] However, the formation of monomeric metallaaziridines from primary amines is unknown. Here we report the first synthetic route to a bridging metallaaziridine (**2**) and its use as a precatalyst for the intramolecular α-alkylation of a primary aminoalkene (eq 1). Reaction development efforts resulted in the identification of a zirconium 2-pyridonate precatalyst for this novel transformation, and preliminary mechanistic investigations suggest bridging metallaaziridine complexes are the key catalytically reactive intermediates.

N,O chelating amidate complexes of group 4 metals are being investigated as a family of modular and tunable hydroamination catalysts.[8] The cyclohydroamination of aminoalkenes can be achieved using group 4 amidate precatalysts that are postulated to form catalytically reactive imido species in situ.[9] However, many group 4 imido complexes also form nitrogen bridged dimers that are presumed to be unreactive for catalytic hydroamination.[10] We demonstrate that such dimeric complexes can undergo directed α-C−H activation to give reactive bridging metallaaziridine complexes. By taking advantage of the enhanced reactivity of a benzylic C−H bond, we have prepared and fully characterized the first example of this unique, reactive structural motif.

Known bis(amidate) titanium hydroamination precatalyst **1**[11] is reacted with 1.5 equiv of benzylamine at 65 °C to give **2** as a dark green solid in 85% recrystallized yield. The solution phase structure of **2** has been confirmed by ^{1}H, ^{13}C, COSY, and HMQC NMR spectroscopic experiments. Notably, a diagnostic resonance at δ 6.15 in the ^{1}H NMR spectrum corresponds to the proton of the bridging metallaaziridine fragment. Single crystals of **2** were grown from pentane; the solid-state molecular structure is shown in Figure 1. This bimetallic species has three bridging ligands: one imido, one amidate, and one bridging metallaaziridine. The C−N bond length for the bridging metallaaziridine is considerably shortened relative to the bridging imido (1.368 Å vs 1.457 Å) and indicative of significant double-bond character, consistent with other reported early transition metal metallaaziridine (η^2-imine) complexes.[6]



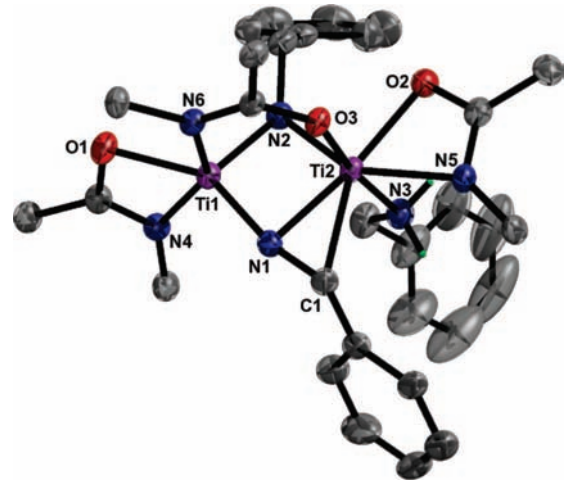


Figure 1. ORTEP representation of the solid-state molecular structure of **2** (ellipsoids plotted at 50% probability, all hydrogens and all except *ipso*-carbons of the amidate ligands removed for clarity) with selected bond lengths (Å), and angles (deg): Ti1−N1, 1.810(2); Ti2−N1, 2.046(2); Ti2−C1, 2.219(3); Ti1−N2, 1.843(2); Ti2−N2, 1.986(2); Ti2−N3, 2.214(2); N1−C1, 1.368(4); C1−Ti2−N1, 37.13(10).

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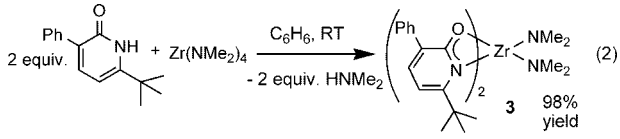
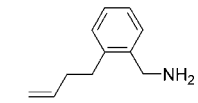
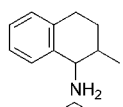
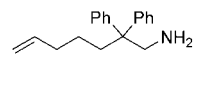
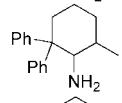
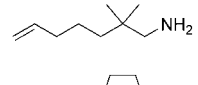
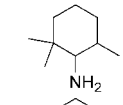
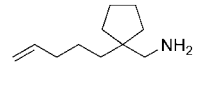
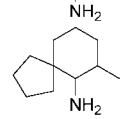
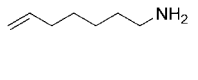
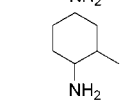
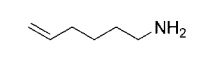
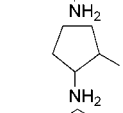
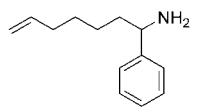
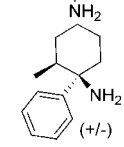
Complex **2** has a reactive M−C bond that can undergo alkene insertion (eq 1) and subsequent catalytic turnover. Unfortunately, all efforts to expand the scope of reactivity with complex **2** were unsuccessful. Thus, to achieve a more readily accessible metal center that could mediate catalytic reactions with multiple substrates, focus shifted to the larger Zr metal center and the less sterically demanding 2-pyridonate ligand. These alternative N,O chelating ligands are known to promote the formation of ligand bridged dimers, as in the classic paddlewheel complexes.[12]

In comparison to noncyclic amidate ligands, substituted 2-pyridonate ligands are an attractive, modular ligand motif that place ligand steric bulk away from the reactive site. This proligand can be efficiently prepared in 3 steps,[13] to give access to a range of substituted pyridones on gram scale. Here we show that 2 equiv of 6-*tert*-butyl-3-phenyl-2-pyridone react cleanly with 1 equiv of $Zr(NMe_2)_4$ to give a monomeric bis(pyridonate) zirconium bisamido (**3**) in excellent yield (eq 2). This precatalyst has been fully characterized by NMR spectroscopy and X-ray crystallography; only monomeric complexes are observed in both solution and solid phases.[14]



(2)

Table 1. Synthesis of Cycloalkylamine Derivatives via Catalytic α-Alkylation with Precatalyst **3**

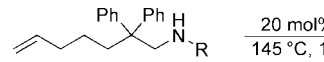
Entry	Aminoalkene	Product	Time (h)	Yield (%) *trans:cis*
1			24[a]	90[d] (3:1)[c]
2			96[a]	63[d] (2:1)[c]
3			24[a]	50[d] (3:1)[c]
4			22[a]	91[d] (2:1)[c]
5			72[b]	43[d] (74)[e] (2:1)[c]
6			20[b]	54[d] (98)[e] (1:2)[c]
7			120[b]	51[f] (1: 19)[c]

[a] 20 mol% catalyst at 145 °C. [b] 40 mol% catalyst at 155 °C. [c] Ratio from ^{1}H NMR spectroscopy. [d] Isolated yield of derivatized products. [e] Consumption of starting material, determined by NMR. [f] NMR yield with 1,3,5-trimethoxybenzene as internal standard.

When using 20 mol% of **3** with various aminoalkenes at high temperature, the intramolecular α-alkylation products of several aminoalkenes can be obtained (Table 1). In entry 1, 1-amino-2-methyltetralin is efficiently prepared with improved diastereoselectivity over complex **2**. Entry 2 shows the formation of the desired α-alkylation product (63% yield), while a 22% yield of the azepane hydroamination product was also obtained. To the best of our knowledge, this is the first report of 7-membered ring formation by group 4 catalyzed hydroamination, indicating that, with some substrates, hydroamination is competitive with α-alkylation using precatalyst **3**.

Notably, when this reaction was attempted at 110 °C with 20 mol% $Ti(NMe_2)_4$ as precatalyst, neither hydroamination nor α-alkylation was observed. This is consistent with earlier reports from the Doye group.[4] Entries 2−4 demonstrate that intramolecular α-alkylation can be enhanced by taking advantage of *gem*-disubstituent effects to facilitate ring closure. However, entries 5 and 6 show that substituents are not required for C−C bond formation; no hydroamination products are observed in these cases (these are known to be challenging substrates for group 4 hydroamination catalysis). Entry 6 demonstrates that this reaction is not limited to the preparation of cyclohexane derivatives. While excellent conversions are observed by NMR spectroscopy for entries 5 and 6, only moderate isolated yields were obtained due to product volatility. Most importantly, entry 7 shows that challenging and sterically demanding quaternary, stereogenic carbon centers can be assembled with excellent diastereoselectivity using this strategy. This primary amine product is a known synthetic precursor to biologically active PCP derivatives.[15]

Interestingly, when using the secondary *N*-methyl or *N*-phenyl aminoalkene substrates (eq 3), no consumption of substrate is observed, even with elevated reaction temperatures and prolonged reaction times. This is in contrast to the Ta catalyzed hydroaminoalkylation reaction, which requires secondary amine substrates.[2] This suggests that Zr imido species are requisite intermediates in the reaction pathway and support a mechanism that accesses a bridging dimer as a precursor to the reactive bridging metallaaziridine complex.



(3)

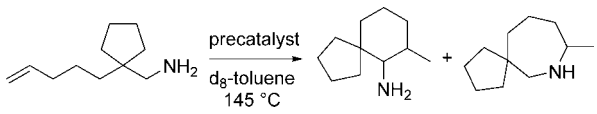
R = Me, Ph

Observations supporting the dimeric nature of the catalytically active complex are seen in Table 2, which shows that varying catalyst loading while maintaining constant substrate concentration affects aminocyclohexane and azepane product distributions. Increased catalyst loading favors the formation of the α-alkylation product, while low catalyst loading gives substantial amounts of hydroamination product (entries 1−4). Furthermore, a direct comparison of entry 4, Table 1 ([catalyst] = 0.1 M) and entry 2, Table 2 ([catalyst] = 0.05 M) shows that increased catalyst concentration results in enhanced C−H activation product formation. Entry 5, Table 2 illustrates that the known Zr complex of the bulkier amidate ligand, *N*-2,2′-diisopropylphenylbenzamidate, which inhibits dimer formation, does not give any observable α-alkylation product but does furnish the hydroamination product in modest yield. Furthermore, consistent with a proposed catalytically reactive bridging metallaaziridine intermediate, complexes without auxiliary ligands, specifically $Zr(NMe_2)_4$ and $Ti(NMe_2)_4$, give the α-alkylation products under these reaction conditions. While these commercially available complexes show promise for this transformation, they do not lend themselves to the development of asymmetric versions of this reaction. Interestingly, preliminary investigations using the Ti congener of pyridonate precatalyst **3** shows no catalytic activity for either hydroamination or α-alkylation.

We propose that dimeric imido complexes, which are thought to be catalytically inactive for hydroamination, are precursors to

the reactive bridging metallaaziridines required for catalytic α-alkylation (Scheme 1). Thus, group 4 complexes that can access reactive monomeric and dimeric imido intermediates can mediate catalytic hydroamination *and* α-alkylation. Here we have demonstrated that by using substrates that do not readily undergo catalytic hydroamination, one can favor the formation of the α-alkylation product over the hydroamination product. However, improvements in catalyst design that promote the formation of bridged dimeric species are anticipated to expand the scope and selectivity of the novel reactivity reported here.

Table 2. Effect of Catalytic Conditions on α-Alkylation (CH) vs Hydroamination (HA) Product Distributions



entry	precatalyst[a]	time (h)	conv (%) (CH/HA)
1	**3**, 40 mol%	6	96 (23:1)
2	**3**, 20 mol%	22	92 (5:1)
3	**3**, 10 mol%	48	86 (3:1)
4	**3**, 5 mol%	148	84 (2:1)
5	$(L)_2Zr(NMe_2)_2$, 20 mol%[c]	115	55 (0:1)
6	$Zr(NMe_2)_4$, 20 mol%	21	87 (10:1)
7	$Ti(NMe_2)_4$, 20 mol%	16	95 (18:1)

[a] [Substrate] = 0.25 M in d_8-toluene. [b] Conversion and ratio of CH/HA from ^{1}H NMR spectroscopy using 0.08 M 1,3,5-timethoxybenzene as internal standard. [c] L = *N*-(2,6-diisopropylphenyl)benzamidate.[9a]

In summary, we have prepared the first example of a group 4 bridging metallaaziridine and demonstrated that the reactive M−C bond formed upon α-C−H activation is susceptible to alkene insertion and catalytic turnover. This novel reactivity has resulted in the synthesis of a new Zr pyridonate precatalyst that promotes catalytic α-C−H functionalization adjacent to the nitrogen of aminoalkene substrates. This new reaction can be added to the growing arsenal of directed sp^3 C−H functionalization reactions[2,16] and is the first example using primary amines as suitable substrates. This approach avoids protection/deprotection steps for the C−C bond formation and can be used in the assembly of amine substituted cycloalkanes. Substrate scope investigations demonstrate that these products can be assembled in good yield with modest diastereoselectivity and ring closure is not dependent upon *gem*-disubstituent effects. Most importantly, quaternary stereogenic centers adjacent to nitrogen can be prepared using this approach. Preliminary mechanistic investigations suggest that α-alkylation is promoted by transiently prepared dimeric zirconium-imido species; trapping experiments and kinetic investigations are ongoing to further elucidate the mechanism of this novel transformation. This mechanistic understanding will assist in catalyst design to achieve enhanced substrate scope and asymmetric versions of this new 100% atom economic C−C bond forming reaction.

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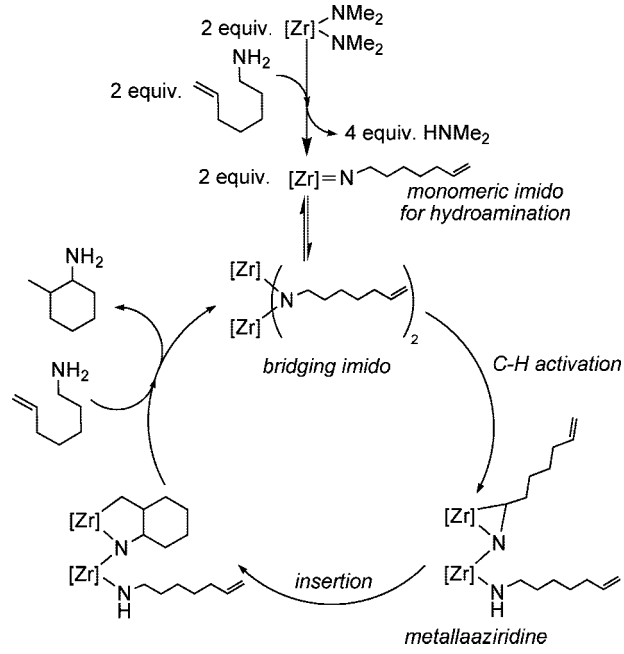
Scheme 1. Proposed Simplified Mechanism for α-C−H Alkylation of Primary Aminoalkenes.



Supporting Information Available: Experimental details, characterization data, and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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