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Broadening the Scope of Group 4 Hydroamination Catalysis Using a Tethered Ureate Ligand

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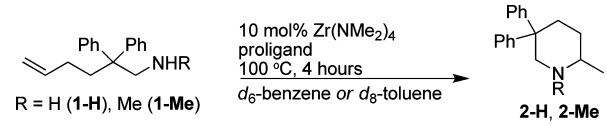
Catalytic hydrofunctionalization reactions are becoming an increasingly powerful method for the formation of carbon-element bonds in an atom economic fashion.[1] One of these reactions, hydroamination, has been intensely investigated and can now be promoted by a wide variety of catalytic systems.[1a,b,d,e,g] Group 4 complexes are among those that have shown great promise for the hydroamination of C−C multiple bonds with primary amines.[2] These catalysts are advantageous over late metal systems due to their low cost and low toxicity and are also preferred over organolanthanide catalysts due to their enhanced stability[3] and improved functional group tolerance.[2c] To date, however, no group 4 systems have been reported for intramolecular alkene hydroamination that compare favorably with other state-of-the-art catalysts.[4] Here we report the use of a simple tethered ureate ligand to support the first example of an easily prepared zirconium precatalyst with excellent reactivity for the intermolecular hydroamination of alkynes and intramolecular hydroamination of alkenes. This includes primary and secondary amine substrates with challenging 1,2-disubstituted unactivated alkenes and polar functional groups.

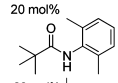
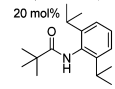
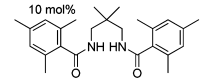
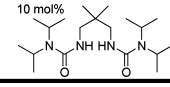
Inspired by the work of Marks[5b] and Odom,[5a] who showed that neutral, sterically accessible zirconium complexes could mediate the hydroamination of secondary aminoalkenes, we sought to develop an easily prepared catalyst for use with both primary and secondary amine substrates. Few group 4 alkene hydroamination catalysts can be used with secondary amine substrates:[2b,5] rare examples include highly sensitive cationic complexes[5c,d] and neutral complexes with modest reactivity.[2b,5a] To the best of our knowledge, no group 4 systems have been previously reported for intermolecular alkyne hydroamination with secondary amines. Thus, broad substrate scope and functional group tolerance remain a challenge in the field.

To address this challenge, we have employed rapidly assembled N,O chelating amidate[2c] and ureate[6] complexes for the preparation of highly electrophilic and catalytically active systems. Table 1 summarizes the results of an *in situ* screen of structurally simple amide and urea proligands with substrates **1-H** and **1-Me**. Notably, in the absence of ligand, $Zr(NMe_2)_4$ gives quantitative conversion of the primary amine substrate (**1-H**) within 4 h at 100 °C but does not result in any detectable product formation using the secondary amine substrate (**1-Me**). Entries 2 and 3 show that increased ligand steric bulk results in reduced reactivity with **1-H**. Most importantly, while all metal and proligand combinations give product **2-H**, only the combinations using the less sterically demanding tethered bis(amide) and bis(urea) (entries 4 and 5) proligands give appreciable formation of **2-Me**.[7] Consistent with previous studies, which have shown that more electropositive metal centers yield more active hydroamination catalysts,[5b,8] the urea proligand in entry 5, incorporating σ-electron-withdrawing substituents, results in the most active catalyst for the conversion of *both* substrates.

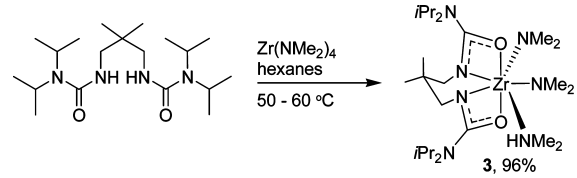
After the identification of an appropriate ancillary ligand, we synthesized the discrete bis(amido) precatalyst. Using a simple protonolysis methodology,[6] complex **3** can be easily prepared on multigram scale from readily available, inexpensive materials in high yield (eq 1). The structure of **3** was fully elucidated, including X-ray crystallographic analysis.[9] Complex **3** can be used for hydroamination catalysis with no change in activity relative to the *in situ* protocol (Table 1, entry 5, isolated yields).

Table 1. In Situ Catalyst Screening of Both Primary and Secondary Aminoalkene Substrates[a]



entry	proligand	conv 1-H (%)[b]	conv 1-Me (%)[b]
1	none	>98	<2
2	20 mol% 	49	<2
3	20 mol% 	5	<2
4	10 mol% 	32	52
5	10 mol% 	>98 (92)	>98 (90)

[a] $[Zr(NMe_2)_4]$ = 0.075 M, [substrate] = 0.750 M. [b] Conversion determined by ^{1}H NMR, number in brackets is isolated yield using 10 mol % **3**.

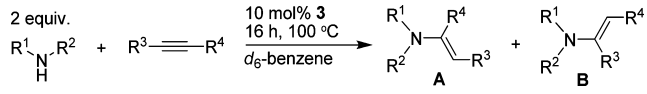


(1)

Based on the promising reactivity displayed by **3** toward secondary aminoalkenes, we postulated that **3** would be effective for the unprecedented group 4 catalyzed intermolecular hydroamination of alkynes with secondary amines (Table 2). Complex **3** mediates these transformations regioselectively with phenyl substituted alkynes (entries 1−5). Notably internal alkynes have reduced reactivity (entries 5 and 6), presumably due to increased steric bulk. The use of morpholine as the reactive secondary amine indicates useful functional group tolerance with this system. With the exception of the sterically unhindered 1-decyne (entries 7 and 8), the reaction is selective for regioisomer **A**. Notably, this precatalyst can be used with primary amines (entry 8) with similar regioselectivities to the corresponding secondary amine example (entry 7).

10.1021/ja906955b

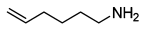
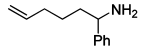
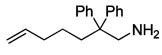
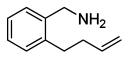
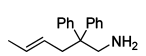
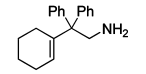
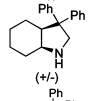
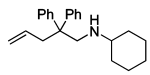
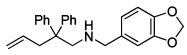
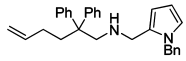
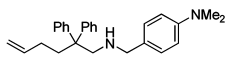
Table 2. Intermolecular Alkyne Hydroamination with Precatalyst **3**[a]



entry	amine	alkyne	yield (%)[b] A	yield (%)[b] B
1	R^1 = Me, R^2 = Bn	R^3 = Ph, R^4 = H	93 (78)	<2
2	piperidine	R^3 = Ph, R^4 = H	80 (68)	<2
3	1,2,3,4-THIQ	R^3 = Ph, R^4 = H	92 (70)	<2
4	morpholine	R^3 = Ph, R^4 = H	97 (82)	<2
5[c]	morpholine	R^3 = Ph, R^4 = Me	57	<2
6[c]	morpholine	R^3 = Ph, R^4 = Ph	44	n/a
7	morpholine	R^3 = C_8H_{17}, R^4 = H	37	44
8[d]	2,6-dimethylaniline	R^3 = C_8H_{17}, R^4 = H	29[e]	54[e]

[a] [**3**] = 0.075 M, [amine] = 1.50 M, [alkyne] = 0.750 M. [b] Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. Number in brackets is isolated yield after reduction. [c] Reaction at 145 °C. [d] Reaction at 110 °C. [e] Yield of imine tautomer.

Table 3. Intramolecular Alkene Hydroamination with Precatalyst **3**[a]

entry	substrate	cond.	product	yield (%)[b]
1		16 h 145 °C		86[c]
2		2 h 145 °C		90 (5:1)[d]
3		20 h 145 °C		90
4		18 h 145 °C		76[e,f]
5		48 h 145 °C		84
6		55 h 145 °C		64[e] (>20:1)[d]
7		15 h 145 °C		91
8		4 h 100 °C		86
9		48 h 100 °C		87
10		28 h 100 °C		89

[a] Reactions in either d_6-benzene or d_8-toluene, [**3**] = 0.075 M, [substrate] = 0.750 M. [b] Isolated yield. [c] Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. [d] Diastereomeric ratio determined by ^{1}H NMR; major isomer shown. [e] Isolated yield of *N*-tosyl derivative. [f] [**3**] = 0.150 M.

Based on these encouraging results, the substrate scope of **3** for intramolecular alkene hydroamination was further explored in known challenging transformations (Table 3).[10] First, complex **3** cyclizes aminoalkenes that do not have *gem*-disubstituents (entries 1 and 2). In addition to 5- and 6-membered rings, **3** also forms azepanes in high yield, an unprecedented result for group 4 hydroamination (entries 3 and 4).[11a] Unactivated internal olefins are known to be very challenging substrates for hydroamination;[2b,3,4a] however, **3** promotes these reactions well (entries 5 and 6). Complex **3** also exhibits moderate to excellent diastereoselectivity (entries 2 and 6). In all cases, no evidence of hydroaminoalkylation side-reactivity is observed; complex **3** is completely chemoselective for hydroamination, contrary to results with other Ti and Zr systems.[2b,11] Several secondary aminoalkenes are also efficiently cyclized by **3** (entries 7−10). Impressively, even a sterically demanding cyclohexyl substituent on nitrogen can be accommodated (entry 7). A commonly cited limitation for highly Lewis acidic catalysts is poor functional group tolerance.[1b] These preliminary results show that **3** is effective in the presence of an acid-sensitive protected catechol, a pyrrole, and a tertiary aniline (entries 8, 9, and 10). These represent the first examples of polar functional group tolerance from a group 4 alkene hydroamination catalyst.

In summary, this work represents a major step forward in the development of a general group 4 hydroamination catalyst, as complex **3** displays significantly expanded substrate scope for both inter- and intramolecular hydroamination and meets or exceeds the activity of other systems.[3] This precatalyst is effective with unactivated internal olefins as well as primary and secondary amines and does not require *gem*-disubstituents for cyclization. Importantly, complex **3** is chemoselective for hydroamination over hydroaminoalkylation.[2b,11] The use of this complex for the hydroamination of alkynes and alkenes with secondary amines implies that Zr imido complexes need not be intermediates for this transformation.[2g] Detailed kinetic and computational investigations are underway to gain mechanistic insight.

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

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(9) See Supporting Information.

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