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Amidate complexes of titanium and zirconium: a new class of tunable precatalysts for the hydroamination of alkynes†

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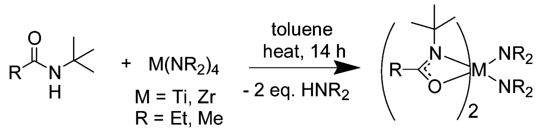
A series of bis(amidate)group 4-bis(amido) complexes have been prepared, characterized and have been shown to be highly tunable precatalysts for both the intra- and intermolecular hydroamination of alkynes.

The catalytic addition of N–H across a carbon–carbon multiple bond is a synthetically important transformation for the preparation of substituted amines and imines. Catalytic hydroamination has been achieved using a variety of transition[1] and f-block[2] metal complexes. In particular, cyclopentadienyl complexes of Ti and Zr have been shown to catalyze the hydroamination of alkynes with primary amines.[3] The development of a flexible catalyst system that takes advantage of the low cost and high reactivity of the group 4 metals while providing enhanced and selective reactivity is a current area of intense investigation. For example, Ti complexes with pyrrole containing auxiliary ligands,[4] guanidinate ligands,[5] and sulfonamidate ligands[6] have been shown to be active precatalysts. Here we report the preparation and characterization of amidate complexes of both Ti and Zr and their application as catalysts for the hydroamination of alkynes. The results presented demonstrate that the reactivity of this class of complexes is dramatically affected by ligand substituents that impact the electronic properties of these precatalysts.

We have identified amidates as a family of easily prepared and highly variable N,O chelating, monoanionic ligands. Their precursors can be prepared from commercially available acid chlorides and primary amines to yield a wide range of crystalline amides that can be varied sterically and electronically. Amidates have been used as bridging ligands for binuclear late transition metal complexes[7] and more recently, have been used as auxiliary ligands for the generation of group 4 olefin polymerization catalysts.[8] One of the challenges of the amidate ligand set is the propensity for complexes bearing these ligands to adopt multiple coordination modes, including monomeric, bridging dimeric and aggregate complexes.[9] Our initial investigations of complexes bearing this ligand type have been restricted to the sterically encumbered *N*-*t*Bu substituted amides, to favour formation of monomeric complexes, while having different groups on the carbonyl of the amide to vary the Lewis basicity (Scheme 1).

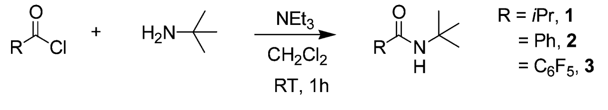
The amide proligands **1**, **2**[10] and **3**[11] were prepared on multigram scale from commercially available acid chlorides and *t*-Bu amine. The crude white crystalline material was further purified and dried by vacuum sublimation to give the desired products in 80–90% yield.

Protonolysis reactions have been used for the preparation of all metal complexes [eqn. (1)]. This route into amidate complexes results in the formation of pentane soluble products that contain largely only one isomer, as indicated by NMR spectroscopy. For example, in the case of the Zr complex of deprotonated **1** with diethylamido ligands the diagnostic *iso*-propyl substituent provides an ideal NMR handle for observing the various isomers in solution. After heating to 100 °C overnight, only one major isomer is observed with diagnostic chemical shifts of a quartet at 3.66 ppm (CH_2 of NEt_2) and a septet at 2.50 ppm (shifted 0.62 ppm downfield from the proligand described above). Furthermore, the integration in all cases is consistent with the desired stoichiometry and the low resolution MS (EI) confirmed the formation of the desired metal complexes. Complexes of **1** are greasy solids that cannot be purified by recrystallization. The complexes prepared from proligands **2** and **3** can be synthesized on multigram scale and are isolated in good yields (60–80%) as yellow to orange microcrystalline solids. The Zr complex prepared from **2** and $Zr(NEt_2)_4$ could not be obtained analytically pure while the Ti derivative prepared from $Ti(NMe_2)_4$ was satisfactory. The Ti complex derived from **3** has been fully characterized including elemental analysis and X-ray crystallographic structure determination.‡ The crystal structure (Fig. 1) reveals a pseudo-octahedral geometry with the diethylamide ligands in a *cis*-orientation, *trans* to the N of the amidate ligands.



(1)

In order to compare the usefulness of our catalyst system with others described in the literature, preliminary results focused on the intramolecular hydroamination of substrate **4** to give the heterocycle **5** [eqn. (2)].[1a] The reactions were carried out in d_6-benzene and monitored by ^{1}H NMR spectroscopy. The results are summarized in Table 1. Here we show that the bis(amidate) complexes of group 4 metals are competent precatalysts for the desired reaction. As expected, the titanium analogues prepared from proligands **1** and **2** are more active catalysts than the zirconium derivatives, such that the titanium complexes catalyzed the reaction at room temperature while zirconium



Scheme 1

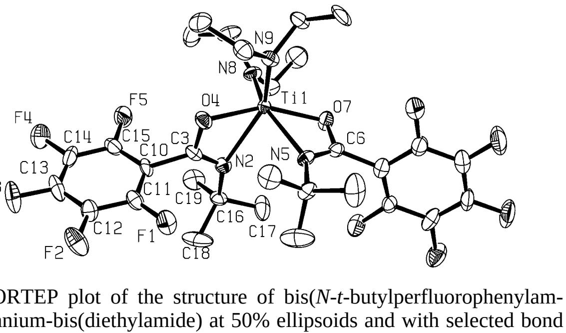


Fig. 1 ORTEP plot of the structure of bis(*N*-*t*-butylperfluorophenylamidate)titanium-bis(diethylamide) at 50% ellipsoids and with selected bond lengths (Å), bond and torsion angles (deg): Ti–N(2), 2.356(7); Ti–O(4), 2.044(6); Ti–N(9), 1.887(7); N(2)–C(3), 1.272(11); O(4)–C(3), 1.307(10); O(4)–Ti–N(2), 59.6(2); N(2)–C(3)–O(4), 117.4(7); O(4)–Ti–O(7), 155.6(3); N(2)–Ti–N(9), 147.9(3); N(2)–C(3)–C(10)–C(15), 94.2(12).

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† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b3/b304176j/

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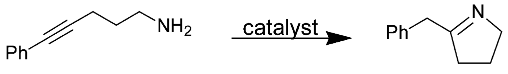
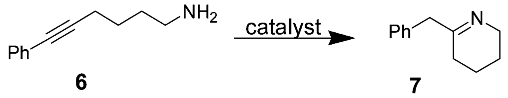
compounds required elevated temperatures. Consequently, only the titanium complex of **3** was prepared. It was noted that the amido ligand (either dimethyl or diethyl amido) did not impact the observed progress of the reaction. This is consistent with the bis(amidate)group 4-bis(amido) complexes being precatalysts and the catalytically active intermediate being a Ti or Zr imido species derived from the primary amine of the substrate, as has been reported for group 4 hydroamination catalysis.[12] Most importantly, we observed that the incorporation of electron withdrawing substituents on the carbonyl moiety of the amidate ligand dramatically enhances catalytic activity. Thus, while the alkyl substituted titanium amidate complex requires 14 h to go to completion, the reaction time is reduced to less than 15 minutes with the pentafluorophenyl derivative (entry 5).



4 **5** (2)

Further comparison of these results with those reported in the literature for Cp_2TiMe_2 (entry 6) and the commercially available $Ti(NMe_2)_4$ (entry 7) shows that our most active catalyst (entry 5) is favourable. In order to directly compare our catalyst with $Ti(NMe_2)_4$ we evaluated both precatalysts using identical reaction conditions on the more challenging substrate **6** to form the six-membered ring product **7** [eqn. (3)]. This experiment demonstrates the high activity of our newly developed catalyst, as this reaction had gone to completion within 3 hours at 40 °C while the $Ti(NMe_2)_4$ catalyst had only gone to 30% completion.



6 **7** (3)

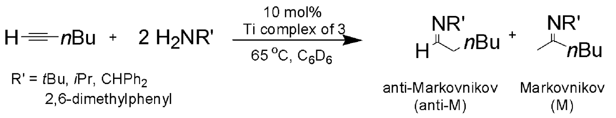
To demonstrate the scope of reactivity of this precatalyst, the Ti complex of deprotonated **3** was used for the more challenging intermolecular hydroamination of alkynes,[12] as summarized in Table 2. Intermolecular hydroamination of terminal alkynes leads to the regioisomeric Markovnikov and anti-Markovnikov products. All reactions were carried out on NMR tube scale with 10 mol% catalyst loading for 24 hours at 65 °C. These results show that intermolecular hydroamination is efficient for terminal alkyl alkynes for both alkyl (entry 1) and aryl amines (entry 4). Interestingly, the regioselectivity of hydroamination changes from a preference for anti-Markovnikov in the case of alkyl amines to Markovnikov in the case of aryl amines. Thus, this catalyst system addresses the synthetically challenging regioselective intermolecular hydroamination of terminal alkynes with alkyl amines.[3b] In contrast, Cp_2TiMe_2 is ineffective for this reaction[12] and $Ti(NMe_2)_4$ is limited to hydroamination using aryl amines.[1g] These preliminary results demonstrate that the Ti complex of **3** is an effective precatalyst for the intermolecular, anti-Markovnikov hydroamination of terminal alkyl alkynes with alkyl amines.

Table 1 Intramolecular hydroamination of alkyne **4** (5 mol% catalyst)

Entry	Proligand	Metal	T/°C	t/h	Yield (%)[a]
1	**1**	Zr	60	24	95
2	**2**	Zr	60	7	98
3	**1**	Ti	25	14	99
4	**2**	Ti	25	3.5	98
5	**3**	Ti	25	0.25	97
6	CpH	Ti	110	4	90[b]
7	$HNMe_2$	Ti	25	0.5	Quant.[6]

[a] NMR conversion *versus* 1,3,5-trimethoxybenzene. [b] Reported yield for the isolated amine product after reduction of imine **5**.[3c]

Table 2 Intermolecular hydroamination of 1-hexyne with various amines



Entry	Amine	Yield (%) (anti-M : M)[a]
1	tBuNH$_2$	93 (99 : 1)
2	iPrNH$_2$	78 (99 : 1)
3	Ph_2CHNH_2	50 (12 : 1)[b]
4	2,6-Dimethylaniline	79 (1 : 99)

[a] Yields determined by NMR using 1,3,5-trimethoxybenzene as internal standard, reaction conditions not optimized. [b] Product ratio confirmed by GCMS.

In summary, we have developed a reliable protocol for the facile preparation of a series of bis(amidate)group 4-bis(amido) complexes. The easily modified amidate ligands allow for significant flexibility in the ligand substituents. Most importantly, they have been shown to be highly tunable precatalysts for both the intra- and intermolecular hydroamination of alkynes. Mechanistic investigations and further elaboration of the amidate ligand to vary reactivity and selectivity in both intra- and intermolecular hydroamination of C–C multiple bonds is on-going, and results will be reported in due course.

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Notes and references

‡ Crystal data: $C_{30}H_{38}N_4O_2F_{10}Ti$, M = 724.54, monoclinic, a = 10.510(1), b = 20.104(2), c = 15.820(1) Å, V = 3342.1(5) Å^3, determined to be a four-component twin with the unit cell parameters given, T = 173 K, space group $P2_1/a$ (#14), Z = 4, μ(MoKα) = 0.35 cm^{-1}, 8086 reflections measured, 4988 unique (R_{int} = 0.072) which were used in all calculations. The final $R(F^2)$ was 0.140 (all data). CCDC 208892. See http://www.rsc.org/suppdata/cc/b3/b304176j/ for crystallographic data in .cif or other electronic format.

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