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Titanium dipyrrolylmethane derivatives: rapid intermolecular alkyne hydroamination

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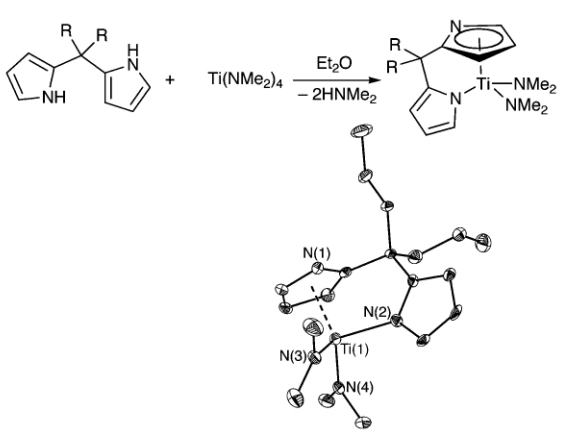
Alkynes are rapidly hydroaminated by primary amines using titanium dipyrrolylmethane derivatives as catalyst.

Generation of imines is most often accomplished through the condensation of ketones or aldehydes with primary amines with a by-product of water. The reaction can be accomplished in a more atom-economical fashion through the hydroamination of alkynes with primary amines.[1] An advantage of the hydroamination procedure is the absence of the water by-product allowing direct addition of another reagent in a one-pot procedure.[2] Furthermore, alkyne hydroamination is studied in the hopes that improved catalysts for olefin hydroamination will be developed, a major challenge for catalysis.[3] Work in titanium-catalyzed alkyne hydroamination also has led to new synthetic protocols for hydrazones, indoles,[4] and α,β-unsaturated-β-iminoamines.[5]

While complexes of many transition metals will catalyze alkyne hydroamination, reactions involving titanium have deservedly drawn attention due to their rapidity, regioselectivity, and ease of use. Titanium hydroamination was pioneered by the intramolecular reactions of Livinghouse and co-workers[6] and early observations of intermolecular hydroamination by Rothwell and co-workers.[7] The groups of Doye,[8] Bergman,[9] and Beller[10] have independently investigated Cp-based catalysts. Ackermann and Bergman[11] described a titanium sulfonamide complex for intramolecular hydroamination. Richeson and co-workers[12] have reported guanidinate catalysts. Commercially available $Ti(NMe_2)_4$ (**1**) is a convenient, rapid catalyst for hydroamination with aryl amines.[13] The pyrrolyl catalyst $Ti(NMe_2)_2$(dpma)[14] (**2**) is a relatively general catalyst for use with alkyl and aryl amines with terminal and internal alkynes.[15]

In an attempt to decrease steric constraints and to increase Lewis acidity of the metal center, we expanded our work on dipyrrolyltitanium complexes[14] to include dipyrrolylmethane derivatives.[16] Treating **1** with 5,5-dimethyldipyrrolylmethane[17] (H_2dmpm) provides $Ti(NMe_2)_2$(dmpm) (**3a**) (Scheme 1).



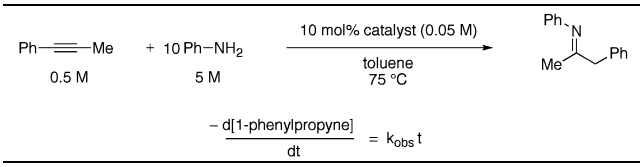
Scheme 1 Synthesis of bis(dimethylamido)(dipyrrolylmethane)titanium complexes (R = Me and Pr), with the solid-state structure of $Ti(dppm)(NMe_2)_2$ (**3b**).

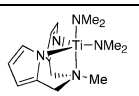
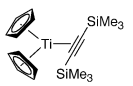
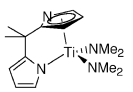
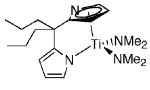
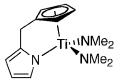
Because of fairly low solubility of **3a** in some common solvents, we also prepared $Ti(dppm)(NMe_2)_2$ (**3b**)† from 5,5-di-*n*-propyldipyrrolylmethane. The solid-state structure‡ of **3b** has one η^5-pyrrolyl and is identical within error to the structure of Cp complex $Ti(C_5H_4CH_2C_4H_3N)(NMe_2)_2$ (**4**) reported by Park and co-workers.[18]

Variable temperature ^{1}H NMR was structurally quite informative. While the pyrrolyl groups in **3a** are inequivalent in the solid-state, the ^{1}H NMR is indicative of fast pyrrolyl exchange in solution at 25 °C. Cooling solutions of **3a** provided a spectrum of an η^5,η^1-dmpm complex. The free energy of activation associated with η^5-pyrrolyl to η^1-pyrrolyl exchange was measured as 10.2 kcal mol^{-1} by VT ^{1}H NMR in CD_2Cl_2.

Table 1 displays kinetic measurements on several different titanium catalysts.[19] The reaction chosen was hydroamination of 1-phenylpropyne with aniline, which is often very clean with a relatively moderate rate. The major, if not exclusive product, is the imine of phenylacetone. The kinetic measurements were done under pseudo-first order conditions with 10 equiv. of aniline to 1 equiv. of 1-phenylpropyne. Because **3a** has relatively low solubility in toluene, hydroamination with this catalyst was run in chlorobenzene. For this particular set of substrates under these conditions, it was observed that $Cp_2Ti(Me_3Si{-}{\equiv}{-}SiMe_3)$ (**5**)[10] was about a factor of two faster than **2**.[15] Still more rapid was commercially available $Ti(NMe_2)_4$ (**1**).[13] Dipyrrolylmethane complexes **3a** and **3b** were an order of magnitude faster than the well explored Cp- and dpma-based

Table 1 Comparison of rate constants for selected catalysts



Entry	Precatalyst		$k_{obs} \times 10^{-6}$ s^{-1}
1		(**2**)	11 [7][a]
2		(**5**)	20 [16][a]
3	$Ti(NMe_2)_4$ (**1**)		76
4		(**3a**)	[157][a]
5		(**3b**)	208 [178][a]
6		(**4**)	1

[a] Values in brackets are with chlorobenzene as solvent.

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Table 2 Alkyne hydroamination results with **3a** as catalyst

Amine	Alkyne	Conditions[a]	% Yield[b]	Selectivity[c]
$PhNH_2$	Bu–≡–H	5%, 25 °C, 5 min	57	40 : 1
	Ph–≡–H	5%, 25 °C, 5 min	41[d]	3.6 : 1[e]
	Ph–≡–Me	5%, 50 °C, 6 h	83	50 : 1
	Et–≡–Et	5%, 50 °C, 24 h	94	
	Ph–≡–Ph	5%, 75 °C, 24 h	84[d]	
$CyNH_2$	Ph–≡–H	5%, 25 °C, 10 min	54	1 : 6[f]
	Ph–≡–Me	5%, 75 °C, 24 h	93	11 : 1
	Et–≡–Et	10%, 75 °C, 48 h	73	
	Ph–≡–Ph	10%, 100 °C, 48 h	72[d]	

[a] Mol% of **3a**, unoptimized reaction time, and temperature. [b] Isolated yield after distillation. [c] Isolated Markovnikov : anti-Markovnikov product. For 1-phenylpropyne the major product is an imine of phenylacetone. [d] Isolated after reduction to amine with excess lithium aluminium hydride in THF. [e] Before isolation, the ratio was 1 : 1.2 by GC/FID. [f] Before isolation, the ratio was 1 : 20 by GC/FID.

catalysts. Reaction rates were slightly slower on a consistent basis in chlorobenzene *versus* toluene.

Because the solid-state structure of $Ti(NMe_2)_2$(dppm) (**3b**) is very similar to Cp-derived **4**, we compared reaction rates between these two complexes. The cyclopentadienyl complex **4** is a relatively poor catalyst and is ~ 100 times slower in reaction rate than **3**. We propose that the pyrrolyl complexes **3** can more readily access an η^1,η^1-configuration, which contributes to the faster reaction rates for **3** relative to **4**.

The results of a short survey of hydroamination reactions with **3a** as catalyst are shown in Table 2.† The reactions were run using chlorobenzene as solvent. All reactions were run with a 1 : 1 solution of alkyne and amine on a 20 mmol scale. The scope of the catalysis is similar to that reported for $Ti(NMe_2)_2$(dpma) with faster reaction times. The only substrate combination tested that was problematic involved cyclohexylamine with 1-hexyne, which led to a greater than usual number of by-products. All other reactions were quite clean. Addition of a terminal alkyne to a solution of 5 mol% **3** and amine at room temperature leads to the reaction vessel becoming hot to the touch from the rapid exothermic reaction. Internal alkynes, however, still required heating and longer reaction times.

We are continuing to explore the applications of these dipyrrolylmethane derivatives in catalysis. The ease with which the ancillary ligand may be altered greatly facilitates investigation into the effect of catalyst design on selectivity and reaction rate.

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Notes and references

† *Synthesis of Ti(dppm)(NMe$_2$)$_2$* (**3b**): In an inert atmosphere dry box, $Ti(NMe_2)_4$ (10 mmol, 2.242 g) in 20 mL ether was added to a near frozen solution of H_2dppm (10 mmol, 2.303 g) in 20 mL ether. The reaction was allowed to warm and stir at 25 °C for 3 h. Volatiles were removed *in vacuo* and the product was recrystallized from toluene/pentane. Orange $Ti(dppm)(NMe_2)_2$ was collected in 68% yield (2.48 g). ^{1}H (C_6D_6, 300 MHz): δ = 0.90 (t, J = 24 Hz, 6H, $CH_2CH_2CH_3$), 1.45 (m, 4H, $CH_2CH_2CH_3$), 2.16 (m, 4H, $CH_2CH_2CH_3$), 2.96 (s, 12H, NCH_3), 6.28 (m, 2H, 3*H*-pyrrolyl), 6.32 (m, 2H, 4*H*-pyrrolyl), 6.95 (m, 2H, 5*H*-pyrrolyl). ^{13}C{^{1}H}: δ = 15.0 ($CH_2CH_2CH_3$), 18.2 ($CH_2CH_2CH_3$), 40.8 ($CH_2CH_2CH_3$), 47.0 (CPr^n_2), 47.6 (NCH_3), 109.6 (3*C*-pyrrole), 111.9 (4*C*-pyrrole), 126.1 (5*C*-pyrrole), 161.5 (2*C*-pyrrole). Elemental analysis for $C_{19}H_{32}N_4Ti$ Found(calculated): C, 62.91(62.63); H, 9.21(8.85); N, 15.25(15.38).

Representative procedure for hydroamination catalyses—aniline and 3-hexyne: Aniline (20 mmol, 1.825 mL), 5% Ti(dmpm)(NMe$_2$)$_2$ (1 mmol, 0.3083 g), and 2 mL chlorobenzene were loaded into a 15 mL pressure tube in an inert atmosphere drybox. To the solution was added 3-hexyne (20 mmol, 2.270 mL) rapidly. The pressure tube was fitted with a Teflon cap and put into a 50 °C oil bath for 24 h. All the volatiles were removed *in vacuo*, and the product was isolated by vacuum distillation in 94% yield (3.30 g). If the alkyne is terminal, the reaction becomes very warm on alkyne addition. The times are for the earliest sampling demonstrating consumption of all starting material by GC/FID. In the case of some imines, purification was facilitated by reduction prior to isolation. In these cases, the imine was reduced with $LiAlH_4$ (60 mmol, 2.27 g) in THF at 65 °C and purified by silica gel chromatography.

Procedure for the kinetic measurements: All manipulations of the solutions were done in an inert atmosphere glove box. In a 2 mL volumetric flask were loaded catalyst (0.1 equiv, 0.500 mL, 0.2 M solution), aniline (10 equiv, 10 mmol), dodecane (1 equiv, 1 mmol), and 1-phenylpropyne (1 equiv, 1 mmol). The solution was diluted to 2 mL with toluene and transferred to a pressure tube. The tube was removed from the dry box and heated in an oil bath at 75 °C. The relative 1-phenylpropyne *versus* dodecane concentration was monitored as a function of time by GC/FID.

‡ *Crystal data* for **3b**: $C_{19}H_{32}N_4Ti$, M = 364.39, monoclinic, a = 9.9440(14), b = 15.266(2), c = 13.696(2) Å, β = 93.252(3)°, U = 2075.8(5) Å^3, $P2(1)/c$, Z = 4, μ(Mo-Kα) = 0.419 mm^{-1}, θ range 2.00–23.28°, 2980 independant reflections (R_{int} = 0.2034). The final $wR(F^2)$ = 0.2273 and $R(F)$ = 0.0876 for reflections $I > 2\sigma$. CCDC reference number 201603. See http://www.rsc.org/suppdata/cc/b2/b212423h/ for crystallographic data in CIF or other electronic format.

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