ORGANOMETALLICS
Communication

Organometallics **2011,** *30,* 921–924 921
DOI: 10.1021/om1011006

Group 5 Metal Binaphtholate Complexes for Catalytic Asymmetric Hydroaminoalkylation and Hydroamination/Cyclization

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Received November 23, 2010

Summary: 3,3′-Silylated binaphtholate tantalum and niobium complexes were shown to be efficient catalysts for the asymmetric hydroaminoalkylation of N-methylaniline derivatives and N-benzylmethylamine with simple alkenes in enantioselectivities of up to 80% ee. No hydroaminoalkylation was observed with aminoalkenes; rather, exclusive asymmetric hydroamination/cyclization took place in up to 81% ee.

Hydroamination[1] and hydroaminoalkylation[2] are two atom-economical processes for the synthesis of valuable industrial and pharmaceutical amines in which an amine N−H bond and an α-amino C−H moiety, respectively, are added across an unsaturated carbon−carbon bond. The hydroamination reaction has been studied intensively, also with respect to asymmetric reactions,[3] and a variety of catalyst systems based on early[2b,4] and late[5] transition metals as well as main-group metals[6] have been developed. However, reports on group 5 metal based hydroamination catalysts have been scarce[7,8] and only the hydroamination of alkynes,[7a,b] allenes,[7a,d] and activated alkenes[7a,c] has been studied. The group 5 metal-catalyzed hydroamination of aminoalkenes has not been reported, to the best of our knowledge, and no niobium-based hydroamination catalysts are known thus far. Furthermore, the only chiral tantalum catalyst system for the asymmetric hydroamination of aminoallenes in up to 34% ee was introduced only very recently.[7d]

Initial reports on hydroaminoalkylation[9] surfaced 30 years ago,[10] but more detailed studies utilizing titanium-,[11] zirconium-,[11c,12] and tantalum-based[13] catalysts have been performed only recently. In several of these studies hydroaminoalkylation was first observed as a side reaction of hydroamination.[11c−e,12,14] While initial catalytic studies[10]

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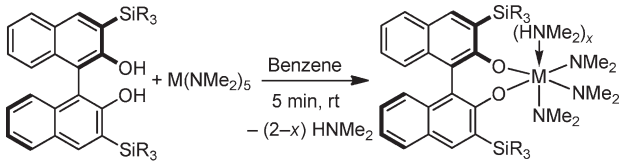
Published on Web 01/12/2011

Scheme 1



	SiR_3
1a	$SiPh_3$
1b	$SiPh_2Bn$
1c	$SiPh_2Me$
1d	$SiMe_2tBu$
1e	$SiMe_3$

	x	M = Ta % yield	M = Nb % yield
2a-M	1	100*	56
2b-M	1	86	74
2c-M	1	76	60
2d-M	0	64	75
2e-M	1	100*	

(* = NMR scale reaction)

suggested that niobium complexes should be viable catalysts, more recent studies have been unsuccessful in confirming this result.[13d] Only two reports on stereoselective hydroaminoalkylation reactions have been reported utilizing chiral tantalum bis(amidate) catalyst systems,[13c,d] and it seems quite astonishing that enantioselectivies of up to 93% ee[13d] could be achieved despite the drastic reaction conditions (130−160 °C).

We envisioned that 3,3′-silylated binaphtholate group 5 complexes[15] may be suitable catalysts for efficient hydroaminoalkylation and/or hydroamination, on the basis of our previous experience with analogous thermally robust[16] and highly enantioselective[17] rare-earth-metal hydroamination catalysts. In this communication we report that niobium complexes are indeed efficient catalysts for asymmetric hydroaminoalkylations and that chiral tantalum complexes are chemoselective catalysts for asymmetric hydroaminoalkylations and hydroamination/cyclizations, depending on the substrates employed in the transformation.

A series of enantiomerically pure (*R*)-binaphtholate tantalum and niobium amido complexes were readily prepared via rapid amine elimination reactions between $M(NMe_2)_5$ (M = Nb, Ta) and the diols **1a**−**e**, containing 3,3′-silyl substituents of various degrees of steric bulk (Scheme 1).[15] While the reactions are quantitative according to NMR spectroscopic analysis, the isolated yields of the niobium complexes are often lower in comparison to those of their tantalum counterparts due to their slightly higher solubility. The complexes generally retain 1 equiv of $HNMe_2$, according to NMR spectroscopy, and the coordinated base could not be removed even after extended heating under vacuum. However, the *tert*-butyldimethylsilyl-substituted complexes **2d-Nb** and **2d-Ta** crystallized in the base-free form and an X-ray crystallographic analysis of the isostructural[18] complexes confirmed a slightly distorted trigonal bipyramidal geometry around the metal (Figure 1).

(15) The synthesis of the tantalum complexes **2a-Ta**, **2c-Ta**, and **2e-Ta** has been previously reported by Rothwell; see: (a) Thorn, M. G.; Moses, J. E.; Fanwick, P. E.; Rothwell, I. P. *Dalton Trans.* **2000**, 2659. (b) Son, A. J. R.; Schweiger, S. W.; Thorn, M. G.; Moses, J. E.; Fanwick, P. E.; Rothwell, I. P. *Dalton Trans.* **2003**, 1620. See also: (c) Weinert, C. S.; Fanwick, P. E.; Rothwell, I. P. *Organometallics* **2002**, *21*, 484. (d) Weinert, C. S.; Fanwick, P. E.; Rothwell, I. P. *Organometallics* **2005**, *24*, 5759.

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(18) Niobium and tantalum both have the identical ionic radius of 64 pm in six-coordinate compounds; see: Shannon, R. D. *Acta Crystallogr.* **1976**, *A32*, 751.

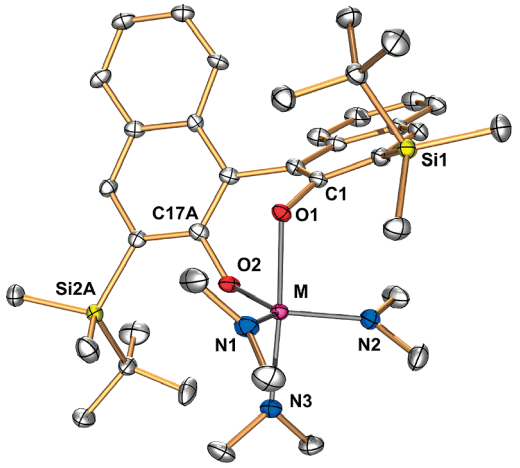
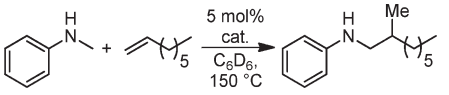


Figure 1. ORTEP diagram of the molecular structure of the isostructural complexes **2d-M** (M = Nb, Ta). Thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms as well as one position of the disordered naphthyl ring and the disordered silane group are omitted for clarity. Selected bond lengths (Å) and angles (deg) for **2d-Nb**: Nb−O1 = 2.0916(9), Nb−O2 = 1.9594(9), Nb−N1 = 1.9528(13), Nb−N2 = 1.9351(12), Nb−N3 = 2.0380(12); O1−Nb−O2 = 85.43(4), O1−Nb−N3 = 172.32(5), O2−Nb−N1 = 125.79(5), O2−Nb−N2 = 114.08(5), O2−Nb−N3 = 97.77(4), N1−Nb−N2 = 119.95(6). Selected bond lengths (Å) and angles (deg) for **2d-Ta**: Ta−O1 = 2.0763(12), Ta−O2 = 1.9478(11), Ta−N1 = 1.9591(15), Ta−N2 = 1.9354(15), Ta−N3 = 2.0303(14); O1−Ta−O2 = 85.10(5), O1−Ta−N3 = 172.27(5), O2−Ta−N1 = 125.36(6), O2−Ta−N2 = 114.80(6), O2−Ta−N3 = 97.46(5), N1−Ta−N2 = 119.61(6). Binaphthyl dihedral angle (deg): 68.5(2) (**2d-Nb**), 68.1(2) (**2d-Ta**).

Table 1. Catalytic Asymmetric Hydroaminoalkylation of 1-Octene with *N*-Methylaniline using Binaphtholate Tantalum and Niobium Complexes[a]

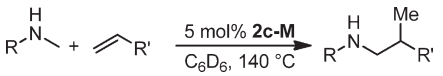


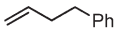
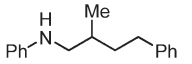
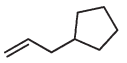
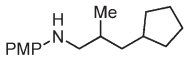
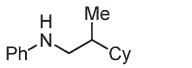
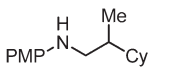
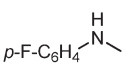
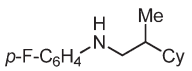
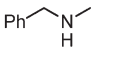
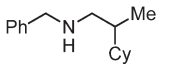
entry	cat.	*T*, °C; *t*, h	yield, %[b]	ee, %[c]
1	**2a-Ta**	170; 48	trace	nd
2	**2a-Nb**	170; 48	trace	nd
3	**2b-Ta**	170; 48	trace	nd
4	**2b-Nb**	170; 48	trace	nd
5	**2c-Ta**	150; 14	88	72
6	**2c-Ta**[d]	150; 14	91	72
7	**2c-Ta**[e]	150; 18	90	71
8	**2c-Ta**	140; 27	85	73
9	**2c-Nb**	150; 7	85	72
10	**2c-Nb**	140; 11	88	73
11	**2d-Ta**	150; 12	79	49
12	**2d-Nb**	150; 8	72	61
13	**2e-Ta**	150; 5	87	34

[a] Conditions (unless otherwise noted): *N*-methylaniline (0.2 mmol), 1-octene (0.8 mmol), cat. (0.01 mmol, 5 mol %), C_6D_6 (0.3 mL), 150 °C, Ar atmosphere. [b] Isolated yield of *N*-benzamide. [c] Determined by chiral HPLC of *N*-benzamide. [d] **2c-Ta** was prepared in situ and was directly used for the catalytic experiment. [e] Conditions: *N*-methylaniline (0.5 mmol), 1-octene (0.75 mmol), cat. (0.05 mmol, 10 mol %), C_6D_6 (0.2 mL). nd = not determined.

For our initial tests on catalytic hydroaminoalkylation we chose 1-octene and *N*-methylaniline as model substrates (Table 1). The catalytic activity of the catalysts significantly decreased with increasing steric bulk of the silyl substituents,

Table 2. Substrate Scope in the Intermolecular Asymmetric Hydroaminoalkylation Catalyzed by 2c-M (M = Ta, Nb)[a]



entry	amine	alkene	product	M	*t*, h	yield, %	ee, %
1				Ta	24	79	67[b]
2				Nb	12	71	70[b]
3				Ta	29	83	71[b]
4				Nb	13	88	71[b]
5				Ta	23	84	75[b]
6				Nb	9	89	80[b]
7				Ta	18	85	74[c]
8				Nb	11	87	75[c]
9				Ta	17	93	73[c]
10				Nb	9	89	73[c]
11				Ta	52	59[d]	35[e]
12				Nb	48	63[f]	25[e]

[a] Reaction conditions (unless noted otherwise): amine (0.2 mmol), alkene (0.8 mmol), **2c-M** (0.01 mmol, 5 mol %), C_6D_6, 140 °C, Ar atmosphere. [b] Determined by chiral HPLC of the corresponding *N*-benzamide. [c] Determined by ^{1}H NMR spectroscopy of (*S*)-Mosher amide. [d] Reaction conditions: 180 °C, 10 mol % cat., 10:1 regioisomer ratio, yield of major regioisomer. [e] Determined by ^{19}F NMR spectroscopy of Mosher amide after benzyl group cleavage. [f] Reaction conditions: 150 °C, 7 mol % cat., 8:1 regioisomer ratio, yield of major regioisomer. PMP = *p*-methoxyphenyl.

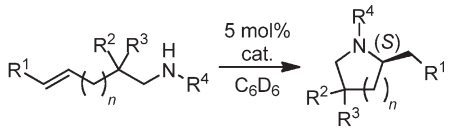
with the most encumbered catalysts **2a**,**b** producing only trace amounts of product even at 170 °C (Table 1, entries 1−4). The sterically less encumbered complexes **2c**−**e** showed good activity at 140−150 °C to form the branched hydroaminoalkylation products exclusively. The sterically least demanding trimethylsilyl-substituted catalyst **2e-Ta** displayed the highest activity but also the lowest selectivity in this series. The niobium complexes were generally more active than their tantalum analogues, but the enantioselectivities were quite comparable. The highest selectivity of 73% ee in this initial screening was observed for the most demanding, yet still active, methyldiphenylsilyl-substituted **2c-Nb** and **2c-Ta** (Table 1, entries 8 and 10).

It should be noted that complexes prepared in situ showed reactivity and selectivity identical with those of analytically pure samples isolated after recrystallization (Table 1, entries 5 and 6). A 4-fold excess of alkene was used in most cases; however, a reduced 1.5:1 alkene to amine ratio and increased substrate and catalyst concentrations resulted in only slightly longer reaction times and comparable selectivity (Table 1, entries 5 and 7). We found that the use of a smaller amount of catalyst and 4 equiv excess of the alkene was more convenient. Therefore, further studies on the scope of the reaction were conducted using these optimized conditions and the most selective catalysts **2c-Ta** and **2c-Nb**.

Table 2 illustrates that the reaction is general for terminal olefins and the reactivity and selectivity patterns are similar for linear, homoallyl, and allyl-substituted alkenes, in remarkable contrast with the case of intermolecular hydroamination, where the sterically more hindered vinylcyclohexane exhibited significantly diminished reactivity.[16] Internal unactivated alkenes, such as cyclohexene, were found to be unreactive. The reaction is unaffected by the presence of electron-withdrawing or electron-donating substituents in the aromatic ring of the *N*-methylaniline substrate (Table 2, entries 5−10). The niobium complex **2c-Nb** displayed systematically higher reactivity in comparison to its tantalum analogue **2c-Ta**. The unsymmetric *dialkylamine* *N*-benzylmethylamine (Table 2, entries 11 and 12) was less reactive than arylalkylamines. Here the difference in reactivity of niobium and tantalum was even more pronounced, with the niobium complex reacting at 150 °C, while tantalum required a significantly higher reaction temperature of 180 °C. The reactions of *N*-methylaniline derivatives provide enantioselectivities in a relatively narrow range of 67−80% ee, while the reaction of *N*-benzylmethylamine was significantly less selective. None of the reactions produced any detectable amount of the linear addition product; however, the reaction of *N*-benzylmethylamine produced the regioisomer originating from activation of the *benzylic* position as a minor byproduct (Table 2, entries 11 and 12). While mechanistic details in this system are scarce, it can be assumed that the reaction proceeds via alkene insertion into a metallaaziridine intermediate, as proposed previously.[10b,11c,13a−13c]

Recent studies on titanium- and zirconium-catalyzed transformations of primary aminoalkenes have shown that the hydroaminoalkylation and hydroamination may occur concurrently, favoring one or the other process depending on the chain length of the aminoalkene.[11c−e,12] The reactivity of group 5 complexes in these reactions has not been reported previously, and to our surprise we discovered that the binaphtholate tantalum complexes readily catalyze the hydroamination/cyclization of various primary aminopentenes and aminohexenes (Table 3), but no hydroaminoalkylation products were detected. The cyclization of the *gem*-diphenyl-activated aminopentene **3a** proceeded with the tantalum catalysts at 100−110 °C with 5 mol % catalyst loading. The highest enantioselectivity for this substrate was 64% ee using the sterically most hindered catalyst **2a-Ta**. Less encumbered complexes showed higher activity but lower selectivity, and the niobium analogue was significantly less reactive (Table 3, entry 2). Other *gem*-dialkyl activated

Table 3. Catalytic Asymmetric Hydroamination/Cyclization of Aminoalkenes using Binaphtholate Tantalum and Niobium Complexes



	n	R^1	R^2	R^3	R^4
3a	1	H	Ph	Ph	H
3b	1	H	-$(CH_2)_5$-		H
3c	1	H	Me	Me	H
3d	2	H	Ph	Ph	H
3e	3	H	Ph	Ph	H
3f	1	Ph	Ph	Ph	H
3g	1	H	Ph	Ph	Bn

4a-g

entry	substrate	cat.	*T*, °C; *t*, h[b]	ee, % (confign)
1	**3a**	**2a-Ta**	100; 16	64 (*S*)[c]
2	**3a**	**2a-Nb**	140; 18	50 (*S*)
3	**3a**	**2b-Ta**	110; 14	< 5% (*S*)
4	**3a**	**2c-Ta**	100; 12	10 (*S*)
5	**3a**	**2d-Ta**	100; 12	< 5 (*S*)
6	**3a**	**2e-Ta**	100; 11	21 (*S*)
7	**3b**	**2a-Ta**	120; 30	81(*S*)
8	**3c**	**2a-Ta**	140; 34	41 (*S*)
9	**3d**	**2a-Ta**	120; 36	17
10	**3e**	**2a-M**[d]	170; 36	[e]
11	**3f**	**2a-Ta**	170; 36	[e]
12	**3g**	**2a-Ta**	170; 36	[e]

[a] Reaction conditions: 5 mol % cat., C_6D_6, Ar atmosphere. [b] > 95% conversion based on ^{1}H NMR spectroscopy using ferrocene as internal standard. [c] 80% isolated yield. [d] M = Ta, Nb. [e] No reaction.

substrates were cyclized with selectivities of up to 81% ee (Table 3, entry 7). Similar to the case for many previous catalyst systems,[19] the cyclization of aminohexene derivatives, such as **3d**, proceeded with significantly diminished selectivity, due to the higher flexibility of the cyclization transition state relative to that of the cyclization of aminopentenes. While the catalytic activity of complexes **2** in the hydroamination/cyclization of aminoalkenes is significantly lower than that of rare earth,[1b,4e,17] alkaline,[20] and alkaline earth metal[6b−e] based hydroamination catalysts, the reactivity is quite comparable to many group 4 metal based catalyst systems.[21] However, there are only a limited number of catalyst systems that provide enantioselectivities exceeding 80% ee in these types of cyclizations.[17,19b,19c,22]

Attempts to cyclize aminoheptene **3e**, 1,2-disubstituted alkenylamine **3f**, or the *secondary* aminoalkene **3g** were unsuccessful. With only a few exceptions,[23] most neutral group 4 metal based catalysts are unable to cyclize *secondary* aminoalkenes, which has been interpreted with a [2 + 2] cycloaddition mechanism analogous to group 4 metal catalyzed alkyne and allene hydroaminations,[24] as the secondary amine does not allow formation of the metal imido species required in this mechanism. However, previous mechanistic studies were unable to confirm an analogous [2 + 2] cycloaddition mechanism in the case of the amine addition to alkynes catalyzed by cationic tantalum imido complexes.[7a,8] Examples of selective azepane ring formation through group 4 metal-catalyzed hydroamination are also rare,[11c,21b,23c] and it is noteworthy that no *hydroaminoalkylation* was observed for **3d**,**e** using either **2a-Ta** or **2a-Nb**, in contrast to the case for group 4 metal based systems,[11c−e,12] which often produce mixtures of hydroamination and hydroaminoalkylation products when applied to aminohexenes or aminoheptenes.

In summary, we have presented herein the first niobium-based chiral hydroaminoalkylation catalyst that achieves enantioselectivities of up to 80% ee. We have also discovered the first group 5 metal based hydroamination catalysts for the asymmetric hydroamination of aminoalkenes with enantioselectivities of up to 81% ee. The hydroaminoalkylation reactivity of the chiral catalysts presented herein is of the same order of magnitude as that of previously studied chiral catalyst systems.[13c,d] The binaphtholate ligands provide a stable coordination environment under these harsh reaction conditions, and a large variety of 3,3′-substituted binaphtholate ligands are readily available in a few synthetic steps starting from inexpensive enantiopure BINOL, which will allow facile catalyst tuning. We are currently performing further catalytic and mechanistic studies[8] toward the scope and limitation of complexes **2** in order to improve the enantioselectivity and reactivity of these new catalysts. In particular, it can be expected that the replacement of amido ligands by electron-withdrawing ligands, e.g. halides,[13b] may lead to more active hydroaminoalkylation catalyst systems.

Acknowledgment. This work was supported by the National Science Foundation through a NSF CAREER Award (CHE 0956021). S.A. thanks the Deutscher Akademischer Austauschdienst (DAAD) for an overseas exchange award. E.G.K. thanks the U.S. Department of Education for a GAANN fellowship.

Supporting Information Available: Text, figures, and tables giving experimental procedures and characterization data, NMR spectra of all new ligands and complexes, Mosher amides, and HPLC traces and CIF files giving crystal data for **2d-Nb** and **2d-Ta**. This material is available free of charge via the Internet at http://pubs.acs.org.

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