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2-Pyridonate Titanium Complexes for Chemoselectivity. Accessing Intramolecular Hydroaminoalkylation over Hydroamination

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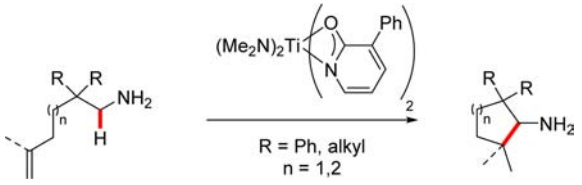
ABSTRACT



Chemoselectivity of intramolecular hydroaminoalkylation over hydroamination has been achieved with a bis(3-phenyl-2-pyridonate) titanium complex. Primary aminoalkenes are selectively α-alkylated by C−H functionalization adjacent to nitrogen to access five- and six-membered cycloalkylamines with a good substrate-dependent diastereoselectivity of up to 19:1.

The development of efficient synthetic routes to amines is highly desired due to their prevalence in biologically active compounds and a vast majority of drugs. An emerging catalytic C−H functionalization method to access higher substituted amines is hydroaminoalkylation,[1] the addition of an sp^3-hybridized α-C−H bond adjacent to nitrogen across a C=C bond (Scheme 1). This atom-economic C−C bond forming reaction has been observed as an unexpected byproduct[2] of intramolecular hydroamination,[3] a C−N bond forming reaction from the addition of an N−H bond across a C=C bond. Both early (groups 4 and 5)[2,4−6] and late (Ir and Ru)[7] transition metal catalysts are able to catalyze the C−C bond forming reaction. The usage of early transition metals[2,4−6] could be advantageous due to their low toxicity and cost and the fact that unprotected amines can be used as substrates.[8]

(1) For a review of hydroaminoalkylation, see: Roesky, P. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 4892.

(2) Müller, C.; Saak, W.; Doye, S. *Eur. J. Org. Chem.* **2008**, 2731.

(3) For a review of hydroamination, see Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795 and references therein.

(4) For Ti catalysts, see: (a) Prochnow, I.; Zark, P.; Müller, T.; Doye, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 6401. (b) Kubiak, R.; Prochnow, I.; Doye, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 1153. (c) Prochnow, I.; Kubiak, R.; Frey, O. N.; Beckhaus, R.; Doye, S. *ChemCatChem* **2009**, *1*, 162. (d) Kubiak, R.; Prochnow, I.; Doye, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 2626. (e) Jaspers, D.; Saak, W.; Doye, S. *Synlett* **2012**, *23*, 2098. (f) Dörfler, J.; Doye, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 1806. (g) Preuss, T.; Saak, W.; Doye, S. *Chem.—Eur. J.* **2013**, *19*, 3833.

(5) For a Zr catalyst, see: Bexrud, J. A.; Eisenberger, P.; Leitch, D. C.; Payne, P. R.; Schafer, L. L. *J. Am. Chem. Soc.* **2009**, *131*, 2116.

(6) For group 5 metal catalysts, see: (a) Clerici, M. G.; Maspero, F. *Synthesis* **1980**, 305. (b) Nugent, W. A.; Ovenall, D. W.; Holmes, S. J. *Organometallics* **1983**, *2*, 161. (c) Herzon, S. B.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 6690. (d) Herzon, S. B.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 14940. (e) Eisenberger, P.; Ayinla, R. O.; Lauzon, J. M. P.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 8361. (f) Eisenberger, P.; Schafer, L. L. *Pure Appl. Chem.* **2010**, *82*, 1503. (g) Zi, G.; Zhang, F.; Song, H. *Chem. Commun.* **2010**, *46*, 6296. (h) Zhang, F.; Song, H.; Zi, G. *Dalton Trans.* **2011**, *40*, 1547. (i) Reznichenko, A. L.; Emge, T. J.; Audörsch, S.; Klauber, E. G.; Hultzsch, K. C.; Schmidt, B. *Organometallics* **2011**, *30*, 921. (j) Reznichenko, A. L.; Hultzsch, K. C. *J. Am. Chem. Soc.* **2012**, *134*, 3300. (k) Payne, P. R.; Garcia, P.; Eisenberger, P.; Yim, J. C.-H.; Schafer, L. L. *Org. Lett.* **2013**, *15*, 2182. (l) Garcia, P.; Payne, P. R.; Chong, E.; Webster, R. L.; Barron, B. J.; Behrle, A. C.; Schmidt, J. A. R.; Schafer, L. L. *Tetrahedron* **2013**, *69*, 5737. (m) Garcia, P.; Lau, Y. Y.; Perry, M. R.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 9144. (n) Zhang, Z.; Hamel, J.-D.; Schafer, L. L. *Chem.—Eur. J.* **2013**, *19*, 8751.

(7) For Ru and Ir catalysts, see: (a) Jun, C.-H.; Hwang, D.-C.; Na, S.-J. *Chem. Commun.* **1998**, 1405. (b) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935. (c) Pan, S.; Endo, K.; Shibata, T. *Org. Lett.* **2011**, *13*, 4692. (d) Bergman, S. D.; Storr, T. E.; Prokopcová, H.; Aelvoet, K.; Diels, G.; Meerpoel, L.; Maes, B. U. W. *Chem.—Eur. J.* **2013**, *18*, 10393. (e) Pan, S.; Matsuo, Y.; Endo, K.; Shibata, T. *Tetrahedron* **2012**, *68*, 9009.

(8) Pyridyl-substitution on the amine is required as a directing group for late transition metal examples.

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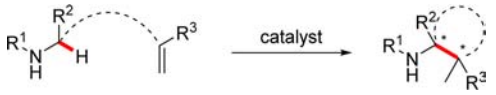
Scheme 1. Hydroaminoalkylation

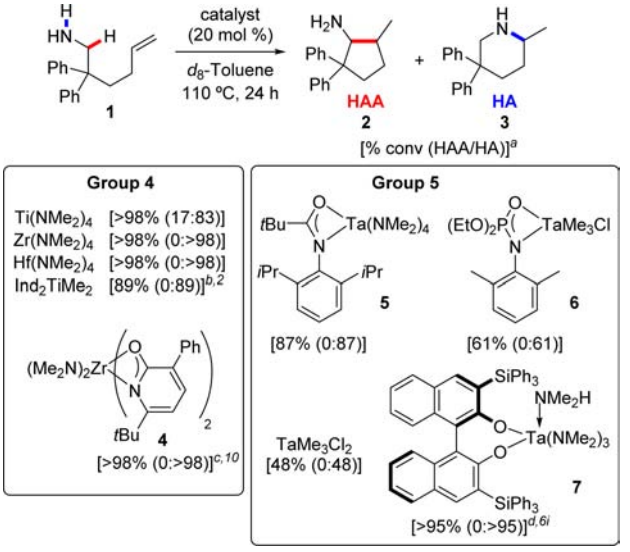


While *intermolecular* hydroaminoalkylation has been achieved with group 5 metals[6] and Ti catalysts,[4b−g] the *intramolecular* variant[2,4a−4c,5] of the reaction remains underdeveloped. To date, limitations include a narrow substrate scope due to hydroamination byproduct formation, low diastereoselectivity, high reaction temperatures (130−160 °C), and long reaction times (up to 96 h). Despite the fact that group 5 systems are able to catalyze the intermolecular transformation with a broad substrate scope and can even mediate asymmetric catalytic reactions,[6e−j] such reactivity has not yet been realized for the intramolecular reaction.[6] Rather, previously reported group 5 intermolecular hydroaminoalkylation catalysts, based on biaryldiamine[6h] or binaphtholate[6i] ligands for example, have been shown to give the intramolecular hydroamination products instead. When targeting hydroaminoalkylation over hydroamination reactivity the high energetic barrier of intermolecular hydroamination ensures that there is no unwanted hydroamination in the intermolecular variant of the reaction.[9] However, in the case of the intramolecular reaction, the hydroamination route is more energetically feasible and typically dominates over hydroaminoalkylation.

Currently, only a handful of group 4 systems, Ti(NMe$_2$)$_4$,[2,4a−4c] Ind$_2$TiMe$_2$,[2] TiBn$_4$,[4c] and bis(6-*tert*-butyl-3-phenyl-2-pyridonate) Zr complex **4**,[5] are known to be reactive for intramolecular hydroaminoalkylation. These catalytic systems have relied on substrate controlled reactivity such that the favorable six-membered-ring hydroaminoalkylation (HAA) product is formed over the challenging seven-membered-ring hydroamination (HA) product. It is desirable to develop catalyst controlled selectivity to access hydroaminoalkylation products preferentially. Herein, we disclose catalyst development efforts to realize the first example of a Ti catalyst that is chemoselective for intramolecular hydroaminoalkylation over hydroamination.

Aminoalkene **1** is a common substrate for hydroamination that is resistant to hydroaminoalkylation (Scheme 2). Thus, it is a good test substrate for examining catalyst controlled selectivity for hydroaminoalkylation over hydroamination. A survey of known group 4 and 5 complexes shows that the formation of the hydroaminoalkylation product **2** over the hydroamination product **3** is rarely observed (Scheme 2). Of these screened complexes, only Ti(NMe$_2$)$_4$ shows the formation of **2** in modest quantities,[2] whereas Zr(NMe$_2$)$_4$ and Hf(NMe$_2$)$_4$ give only the formation of **3**. While Ind$_2$TiMe$_2$ is a useful catalyst for the intermolecular hydroaminoalkylation of alkenes,[4d,g] it promotes hydroamination (**3**) over hydroaminoalkylation (**2**) with intramolecular substrate **1**.[2] Our previously reported Zr pyridonate complex **4** is a good catalyst for substrate controlled intramolecular hydroaminoalkylation,[5] but with **1**, it also promotes hydroamination preferentially, as only **3** was observed.[10] Furthermore, our reported *N,O*-chelated Ta intermolecular hydroaminoalkylation catalysts, **5**,[6e,f,k] and **6**,[6m] as well as TaMe$_3$Cl$_2$,[6n] and Hultzsch's binaphtholate system **7**,[6i] give only **3** as the product. Given that only Ti showed promise for the formation of **2**, Ti was chosen for further investigation.

Scheme 2. Comparison of Reported Groups 4 and 5 Precatalysts for both Hydroaminoalkylation (HAA) and Hydroamination (HA) Reactions



[a] Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [b] 5 mol %, 105 °C. [c] 10 mol %, 5 h. [d] 5 mol %, 120 °C, 36 h, C_6D_6.

Initial investigations focused on exploring the reactivity of *N,O*- and *N,N*-chelated Ti complexes for reactivity with substrate **1** (Table 1). Related ligand sets have been employed for the development of intermolecular hydroaminoalkylation precatalysts.[4e,f,5,6e−h,6k−m] A screening of amidate complexes[11,12] (Table 1, entries 1 and 2) and a ureate complex[13] (Table 1, entry 3) shows that simple amidate and ureate ligand sets are not good for intramolecular hydroaminoalkylation, as only hydroamination product **3** is observed. A bulky mono(2-aminopyridinate) complex[14] also gives **3** as the only product (Table 1, entry 4). However, using 2-aminopyridinate complexes generated

(9) Currently, there is no report of group 4 or 5 metal catalyzed intermolecular hydroamination in the literature.

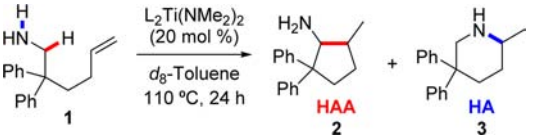
(10) Bexrud, J. A.; Schafer, L. L. *Dalton Trans.* **2010**, *39*, 361.
(11) Webster, R. L.; Noroozi, N.; Hatzikiriakos, S. G.; Thomson, J. A.; Schafer, L. L. *Chem. Commun.* **2013**, *49*, 57.
(12) Thomson, R. K.; Zahariev, F. E.; Patrick, B. O.; Wang, Y. A.; Schafer, L. L. *Inorg. Chem.* **2005**, *44*, 8680.
(13) Leitch, D. C.; Beard, J. D.; Thomson, R. K.; Wright, V. A.; Patrick, B. O.; Schafer, L. L. *Eur. J. Inorg. Chem.* **2009**, 2691.
(14) Chong, E.; Qayyum, S.; Schafer, L. L.; Kempe, R. *Organometallics* **2013**, *32*, 1858.

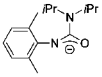
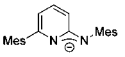
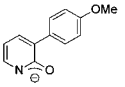
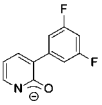
in situ with less sterically demanding *N*-methyl-2-aminopyridine[4f] shows that a 1:2 mixture of $Ti(NMe_2)_4$ and the proligand is more selective for hydroaminoalkylation than a 1:1 mixture (Table 1, entry 5). To extend our investigation of 2-pyridonate group 4 complexes[5,10,11] and modify **4** for enhanced reactivity, bis(2-pyridonate) Ti complexes have been synthesized by reacting $Ti(NMe_2)_4$ with various 2-pyridones (2 equiv), and crude products[15] have been used for catalytic screening (Table 1, entries 6−13). The Ti analogue of **4** with bulky 3,6-disubstituted pyridonates shows poor reactivity (Table 1, entry 6). Some steric bulk promotes favorable reactivity, as simple 2-pyridonate shows a preference for hydroaminoalkylation over hydroamination, but low conversion is observed with unidentified side products (Table 1, entry 7). The location of the steric bulk is shown to be critical. 6-Methylpyridonate (Table 1, entry 8) is unfavorable, while 3-methylpyridonate (Table 1, entry 9) increases conversion to the desired hydroaminoalkylation products. To our delight, 3-phenylpyridonate shows a dramatic improvement in selectivity for hydroaminoalkylation (Table 1, entry 10). Increasing the steric bulk at position 3 with a mesityl substituent disfavors reactivity (Table 1, entry 11). In probing the importance of electronic effects, an electron-donating 4-methoxyphenyl substituent (Table 1, entry 12) shows negligible influence on hydroaminoalkylation reactivity over the phenyl substituent (Table 1, entry 10), but an electron-withdrawing 3,5-difluorophenyl substituent increases the unwanted hydroamination reactivity (Table 1, entry 13).

With 3-phenyl-2-pyridonate chosen as the ideal ligand for the reaction, the bis(2-pyridonate) Ti complex **8** has been synthesized (*vide supra*) and characterized.[16] The solid-state molecular structure of **8** reveals an *O-trans* C_2-symmetric structure with a distorted octahedral coordination about the Ti center and both ligands bound in a κ^2-binding mode (Figure 1). Asymmetric binding of the *N,O*-ligand [Ti−O_{avg} 2.0268(12) Å; Ti−N_{avg} 2.2567(14) Å] is observed,[16] in agreement with previously reported 2-pyridonate group 4 complexes.[5,10,11]

Complex **8** displays catalyst controlled preferential formation of both five- and six-membered cycloalkylamines from primary aminoalkenes, rather than *N*-heterocyclic hydroamination products (Table 2). An overall catalyst loading of 20 mol % is added in two batches of 10 mol % to overcome the observed slow decomposition of catalyst over the course of the reaction.[17] Good reactivity of **8** at temperatures as low as 110 °C is feasible, in comparison to $Ti(NMe_2)_4$ and $TiBn_4$ that require temperatures in the range of 130−160 °C.[4a−c] For the synthesis of cyclopentylamines (Table 2, entries 1−3), the *cis* diastereomer is formed preferentially with good selectivity (up to 10:1). This compares favorably with previous reports (*dr* = 4:1) where the hydroaminoalkylation products are observed only as side products of hydroamination.[2] Impressively, disubstituted alkenes can undergo hydroaminoalkylation

Table 1. Screening of *N,O*- and *N,N*-Ligands on Titanium[a]



entry	L	conv (%)[b]	HAA/HA[b]
1		91	0:91
2		58	0:58
3		8	0:8
4[c]		>98	0:>98
5[d]		(97)[e] 87	(20:77)[e] 52:35
6		3	n.d.
7		9	8:1
8		4	n.d.
9		45	37:8
10		76	71:5
11		16	8:8
12		75	70:5
13		86	54:32

[a] [Substrate] = 0.25 M. [b] Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. n.d. = not determined. [c] $LTi(NMe_2)_3$. [d] *In situ* prepared complex. [e] Using a 1:1 mixture of $Ti(NMe_2)_4$ and LH.

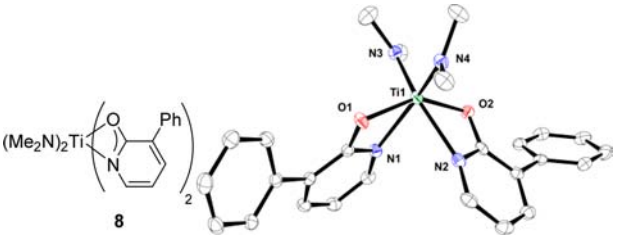


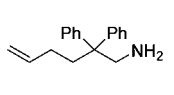
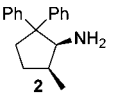
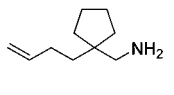
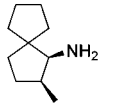
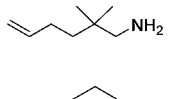
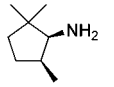
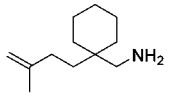
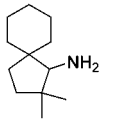
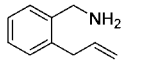
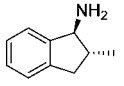
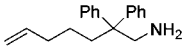
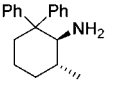
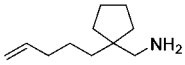
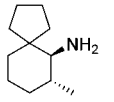
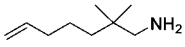
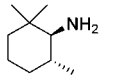
Figure 1. ORTEP representation of the solid-state molecular structure of **8** plotted with 50% probability ellipsoids for non-hydrogen atoms. Benzene solvent molecule omitted for clarity.

(15) Crude complexes are of sufficient purity, and ^{1}H NMR spectra show single products.

(16) See Supporting Information.

(17) Monitoring of the reaction as a function of time shows a marked decrease in the rate of conversion over time.

Table 2. Intramolecular Hydroaminoalkylation of Primary Aminoalkenes with **8**[a]

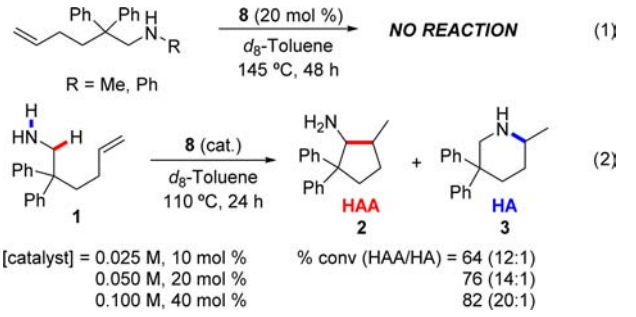
entry	substrate	(±) product	yield (%)[b]	*trans*/*cis*[c]
1		 **2**	73[d]	1:5
2			67[e,f]	1:10
3			53[e,f]	1:7
4			72[f]	-
5[g]			70[d,f]	3:1
6[h]			79[e]	10:1
7[h]			76[e,f]	9:1
8[h]			75[e,f]	19:1

[a] Reaction conditions: substrate (0.60 mmol), **8** (2 × 10 mol %), toluene (2.4 mL), 110 °C, t = 48 h. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy prior to chromatography. [d] Yield of combined diastereomers. [e] Yield of diastereomer illustrated. [f] Derivatized prior to isolation. [g] 130 °C. [h] 145 °C.

intramolecularly for the first time (Table 2, entry 4). Interestingly, the formation of the *trans* isomer is favored in the formation of 1-aminoindane (Table 2, entry 5). For the synthesis of cyclohexylamines (Table 2, entries 6−8), excellent diastereoselectivity (up to 19:1) for the *trans* isomer is observed. These results are a significant enhancement over previously reported results (dr < 5:1).[4c,5]

It was noted that secondary *N*-methyl or *N*-phenyl aminoalkene substrates are unreactive with **8** at 110 °C or at 145 °C (Scheme 3, eq 1). This observation suggests that Ti imido species could be involved as intermediates in the catalytic cycle, as has been proposed for the related Zr(2-pyridonate) complexes.[5] Furthermore, an increase in

Scheme 3. Evaluation of Secondary Aminoalkene Substrates and Effect of Catalyst Concentration with **8**



catalyst concentration further increases the chemoselectivity for hydroaminoalkylation over hydroamination (Scheme 3, eq 2). These observations are consistent with the previously reported formation of dimeric imido species, which are proposed to be unreactive for hydroamination, but may promote hydroaminoalkylation via bridging metallaziridine intermediates.[5,16]

In summary, we have shown for the first time that intramolecular hydroaminoalkylation of primary aminoalkenes can be achieved selectively over hydroamination using bis(3-phenyl-2-pyridonate) Ti complex **8** to access both five- and six-membered cycloalkylamines. Furthermore, a noticeable improvement in diastereoselectivity of up to 19:1 has been realized by utilizing the small Ti metal center in combination with 3-substituted-2-pyridonate ligands. Mechanistic investigations are currently ongoing to elucidate reactive intermediates and rationalize the observed diastereoselectivities of the reaction. These mechanistic insights will assist in the development of new catalysts with enhanced catalytic efficiency and stereoselectivities.

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

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