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Tantalum Catalyzed Hydroaminoalkylation for the Synthesis of α- and β-Substituted *N*-Heterocycles

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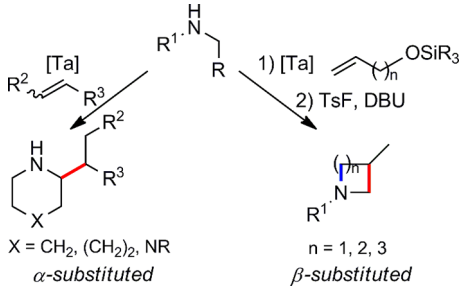
ABSTRACT



Unprotected secondary amines are directly alkylated by C−H functionalization adjacent to nitrogen, thereby opening new routes toward the synthesis of α- and β-alkylated *N*-heterocycles. α-Alkylated piperidine, piperazine, and azepane products are prepared from heterocycles and alkenes in an atom-economic reaction with excellent regio- and diastereoselectivity. β-Alkylated *N*-heterocycles are synthesized via a scalable one-pot alkylation/cyclization procedure generating 3-methylated azetidines, pyrrolidines, and piperidines.

Saturated *N*-heterocycles are key structural elements found in a wide variety of natural products,[1] pharmaceuticals,[2] and agrochemicals[3] (Figure 1).[4,5] Consequently, the rapid and selective alkylation of these compounds from simple, inexpensive, readily available chemicals is an attractive route for their preparation. To this end, catalytic C−H functionalization has emerged as a selective and powerful tool for the direct alkylation of sp^3 hybridized C−H bonds adjacent to the nitrogen of amine substrates.[6] The current state-of-the-art approach for the direct alkylation and arylation of saturated *N*-heterocycles has focused on stoichiometric α-lithiation strategies,[7] radical-based C−H activation,[8] photoredox functionalization,[9] ruthenium catalyzed α-alkylation and arylation,[10] Cu-catalyzed cross-dehydrogenative couplings (CDC),[11,6b] and metal-catalyzed carbene insertions.[12] To date, these strategies all require stoichiometric reagents, activated substrates, and/or

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(7) These include coupled α-lithiation/electrophilic substitution, as well as α-lithiation/transmetalation/palladium cross coupling: (a) Seel, S.; Thaler, T.; Takatsu, K.; Zhang, C.; Zipse, H.; Straub, B. F.; Mayer, P.; Knochel, P. *J. Am. Chem. Soc.* **2011**, *133*, 4774. (b) Beng, T. K.; Gawley, R. E. *Org. Lett.* **2011**, *13*, 394. (c) Barker, G.; McGrath, J. L.; Klapars, A.; Stead, D.; Zhou, G.; Campos, K. R.; O'Brie, P. *J. Org. Chem.* **2011**, *76*, 5936. (d) Coldham, I.; Raimbault, S.; Whittaker, D. T. E.; Chovatia, P. T.; Leonori, D.; Patel, J. J.; Sheikh, N. S. *Chem.—Eur. J.* **2010**, *16*, 4082. (e) Barker, G.; O'Brien, P.; Campos, K. R. *Org. Lett.* **2010**, *12*, 4176. (f) O'Brien, P.; Bilke, J. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 2734.

(8) For selected examples see: (a) Yoshimitsu, T.; Matsuda, K.; Nagaoka, H.; Tsukamoto, K.; Tanaka, T. *Org. Lett.* **2007**, *9*, 5115. (b) Yoshimitsu, T.; Arano, Y.; Nagaoka, H. *J. Am. Chem. Soc.* **2005**, *127*, 11610. (c) Suga, S.; Suzuki, S.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2002**, *124*, 30.

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10.1021/ol400729v
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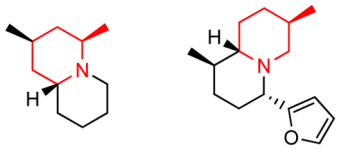
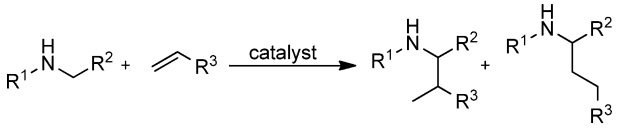


Figure 1. Natural products containing an α- or *β*-alkylated *N*-heterocyclic core.[4,5]

protecting/directing groups on the nitrogen substituent. A complementary and atom economic strategy for alkylation at the α-position of unprotected secondary amines is early transition-metal catalyzed hydroaminoalkylation (Scheme 1).[13]

Scheme 1. Intermolecular Hydroaminoalkylation



To date, hydroaminoalkylation investigations using group 4 and 5 based catalyst systems have shown that secondary arylalkyl and dialkyl acyclic amines can be efficiently prepared.[14] Indeed, substrate scope investigations of such recently developed systems have repeatedly shown that the only *N*-heterocycle that can undergo direct C−H functionalization is 1,2,3,4-tetrahydroquinoline.[14e,i,k,m] One reported example of the hydroaminoalkylation of piperidine (Table 1, entry 1) was disclosed by our group over 3 years ago using Ta amidate precatalyst **1** (Figure 2).[14i] Since that time, several catalyst development reports have conceded that reactivity with cyclic dialkylamine substrates is particularly challenging.[14a,b,d,k] Furthermore, ongoing catalyst development efforts in our laboratories have shown that the amidate supported tantalum complex **1** promotes unique reactivity, as we have developed new catalysts with improved activity and alkene substrate scope that cannot be used with piperidine.[15] Here we explore the broader substrate scope of this unique reactivity identified for Ta amidate precatalyst **1**. The direct α-alkylation of piperidines is explored and reactions with azepanes and piperazines are disclosed for the first time. The improved functional group tolerance observed during these investigations also promoted the development of a one-pot synthesis of *β*-methylated aminoalcohols, azetidines, pyrrolidines, and piperidines featuring hydroaminoalkylation as a key step in their syntheses.

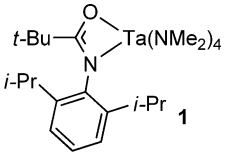


Figure 2. Tantalum amidate precatalyst **1**.

The exploration of substrate scope builds upon the single previous report of using piperidine for the hydroaminoalkylation of 1-octene (Table 1, entry 1).[14i] Typically, pyrrolidines are preferred over piperidine substrates for α-lithiation strategies[7e,10c,16] and Ru catalyzed α-alkylation.[10a] Thus the direct alkylation of larger *N*-heterocycles such as piperidines and azepanes presented here is complementary to other established approaches. Using 5 mol % of **1**, an internal alkene, norbornene, can undergo hydroaminoalkylation with piperidine (Table 1, entry 2). Protected alcohols can be incorporated into the alkene, providing a site for further functionalization of the amine product (Table 1, entry 3). Alternatively, a piperidine with a protected carbonyl substituent is shown to be compatible with this early transition metal catalyst (Table 1, entry 4).

With such functional group tolerance established for **1**, 1,2,3,4-tetrahydroquinoline can be used for the hydroaminoalkylation of olefinic silyl ethers (Table 1, entries 5, 6). Impressively, larger heterocyclic rings such as azepane can also be used, however decreased diastereoselectivity is observed (Table 1, entry 7). The direct alkylation of *N*-substituted piperazines was then explored (Table 1, entries 8−12).[17] Remarkably, this reaction is tolerant to various substituents on the distal nitrogen, including *p*-methoxyphenyl and benzhydryl which allow for subsequent deprotection. Good yields are obtained with both alkyl and benzylic olefins (Table 1, entries 11, 12). Efforts to directly alkylate

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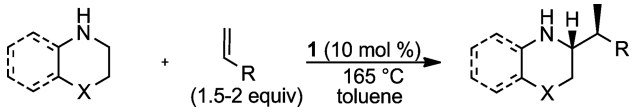
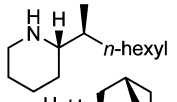
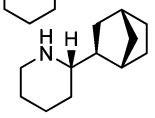
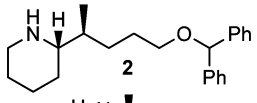
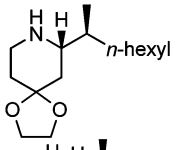
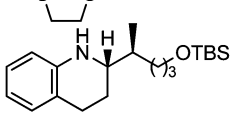
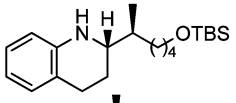
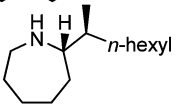
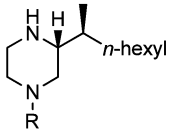
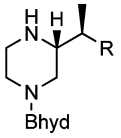
(17) Attempted hydroaminoalkylation with parent piperazine, morpholine, and thiomorpholine was unsuccessful.

Table 1. Hydroaminoalkylation of Saturated *N*-Heterocycles



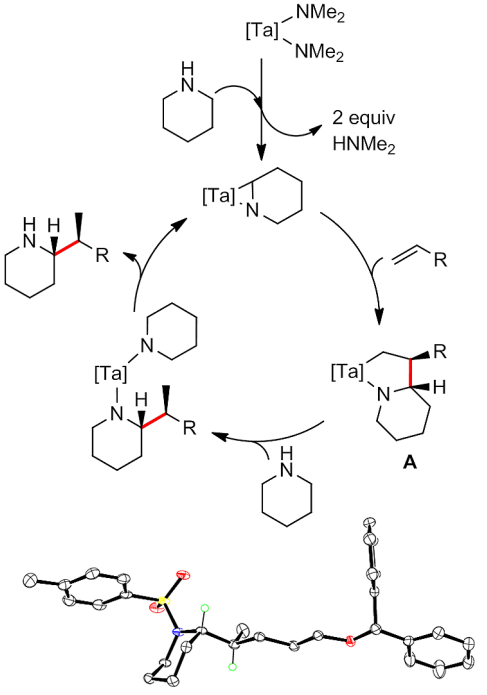
entry	product (+/-)[a]	*t* (h)	yield (%)[b]	dr[c]
1		143	76	>20:1
2		72	79	>20:1
3		96[d]	26	>20:1
4		69	59	>20:1
5[e,f]		165	64	>20:1
6[e,f]		118	78	>20:1
7		72	60	10:1
8	 R = Me	72	43	>20:1
9	Ph	72	68	>20:1
10	PMP	69	69	>20:1
11	 R = *n*-hexyl	72	46	>20:1
12	Bn	72	84	>20:1

[a] Stereochemistry assigned by analogy to **2**. TBS, *tert*-butyldimethylsilyl; Cy, cyclohexyl; Bn, benzyl; PMP, *p*-methoxyphenyl; Bhyd, benzhydryl. [b] Isolated after *N*-tosylation. [c] Determined by ^{1}H NMR spectroscopy of isolated product. [d] Reaction time was not optimized. [e] Reaction at 145 °C and product isolated as the free amine. [f] 5 mol % **1**.

5-membered *N*-heterocycles such as pyrrolidine and indoline were not successful and catalyst decomposition was observed.[18]

In all cases the regio- and diastereoselectivity of this transformation is excellent and typically only one isomer is detected when monitoring the reaction by NMR spectroscopy. Upon the basis of the mechanistic proposal for hydroaminoalkylation (Scheme 2),[14b,i,n] excellent selectivity is anticipated due to the proposed formation of metallacyclic intermediates. Regioselective alkene insertion into the strained metallaziridine intermediate has been consistently observed for group 5 hydroaminoalkylation.[14b,d,f,i,l,m] In the case of hydroaminoalkylation with heterocycles, the alkene substituent R would be proposed to be on the opposite face of the 5-membered metallacyclic intermediate **A** formed with the heterocyclic ring. This would result in both regioselective and diastereoselective hydroaminoalkylation with *N*-heterocyclic substrates. Indeed, this selectivity proposal has been confirmed by X-ray crystallography. Derivitization of the crude product of Table 1, entry 3 with *p*-toluenesulfonyl chloride generated a white solid **2** that could be recrystallized for rigorous analysis (Scheme 2). The solid state molecular structure shows the formation of the anticipated diastereomer of the branched, monoalkylated product.

Scheme 2. Postulated Mechanism for Tantalum Catalyzed Hydroaminoalkylation and ORTEP Representation of the Solid-state Molecular Structure of **2**[a]



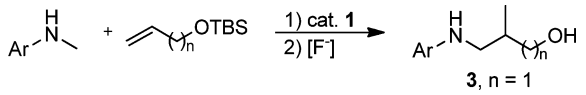
[a] Ellipsoids plotted at 50% probability, only select hydrogens shown.

Product yields are variable and unreacted heterocyclic starting materials can be observed upon reaction completion. Interestingly, no over alkylation is observed under these rather forcing reaction conditions, even in the presence of excess alkene. This selective monoalkylation can be rationalized based upon the sensitivity of this catalyst system to steric bulk. For example, no reaction is observed when using 2-methylpiperidine and 1-octene with these reaction conditions.

Hydroaminoalkylation precatalyst **1** can be used to efficiently prepare a variety of α-alkylated *N*-heterocycles (Table 1). Scheme 1 shows that selectively *β*-methylated acyclic amines can be prepared using hydroaminoalkylation. The functional group tolerance of precatalyst **1** suggested

(18) Red precipitates observed following addition of indoline and fully characterized. See Supporting Information.

Scheme 3. Synthesis of β-Methylated γ-Aminoalcohols by Hydroaminoalkylation



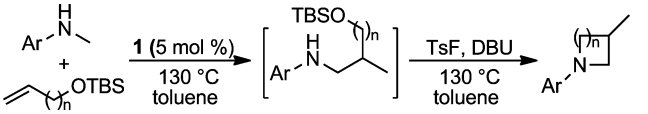
that hydroaminoalkylation could also be used for the catalytic synthesis of β-methylated aminoalcohols (Scheme 3) and β-methylated *N*-hetereocycles (Table 2).

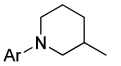
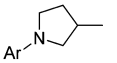
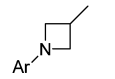
As shown in Scheme 3, various β-methylated aminoalcohols can be prepared by the hydroaminoalkylation of alkenes with *t*-butyldimethyl silyl protected alcohol substituents and subsequent deprotection. Notably, here we report the first example of hydroaminoalkylation of an allylalcohol derivative with *N*-methyl-*p*-methoxyaniline. After deprotection, the β-methylated γ-aminoalcohol **3** is isolated in 91% yield.

Alternatively, rather than a simple deprotection, the conversion of the silyl protected alcohol into a suitable leaving group for nucleophilic substitution was envisioned, using the recently developed method of Gembus.[19] Thus, β-methylated *N*-heterocycles can be prepared using a one-pot method with commercially available *p*-toluenesulfonyl fluoride to install a leaving group *in situ* (Table 2). We examined first the α-alkylation and cyclization using *N*-methylaniline and *t*-butyldimethyl(pent-4-enyloxy)silane (Table 2, entry 1). After full conversion of the starting amine, using 5 mol % of **1**, to the alkylated intermediate, as monitored by ^{1}H NMR spectroscopy, TsF and DBU can be added directly to the reaction mixture and then warmed to 130 °C for cyclization. This transformation is also applicable to anilines bearing electron donating and withdrawing substituents (Table 2, entries 2, 3). Most importantly, this synthetic approach has been shown to be ammenable to gram scale reactions (Table 2, entries 2, 3). The possibility of incorporating aryl halogen containing substrates is attractive due to the high utility of such functionalities in late transition metal catalyzed synthetic transformations (Table 2, entry 3). Entries 4 and 5 show that pyrrolidines can also be accessed. Notably, this procedure is even applicable to the construction of small, strained rings such as methylated azetidines (Table 2, entry 6).

Such β-substituted *N*-heterocycles are of particular interest as they are present in the cores of natural products, and their efficient, modular syntheses are desirable from a

Table 2. One-pot Synthesis of β-Methyl *N*-Heterocycles



entry	Ar	n	product	yield (%)[a]
1	Ph	3		67
2	PMP			67[b]
3	*p*-Cl Ph			57[b]
4	PMP	2		72
5	Ph			69
6	PMP	1		48

[a] Isolated yields. [b] Performed on gram scale.

medicinal chemistry perspective.[20] These preliminary results show that hydroaminoalkylation affords an alternative disconnection for the general and straightforward access to β-methylated azetidines, pyrrolidines, and piperidines.

In summary, we have shown that hydroaminoalkylation can be used as a key synthetic step in substituted heterocycle synthesis. Two complementary methods to access α- and β-substituted *N*-heterocycles, as well as β-methylated aminoalcohols from simple amine and alkene starting materials have been explored. The α-C−H activation/alkylation of unprotected piperidine, piperazine, and azepane substrates with precatalyst **1** proceeds with excellent selectivity generating one diastereomer of the branched product. The formation of β-methylated azetidine, pyrrolidine, and piperidine compounds in an alkylation/cyclization, one-pot procedure highlights an alternative approach for the synthesis of these medicinally relevant compounds. On-going work focuses on catalyst development to reduce reaction times and temperatures, improve substrate scope, and functional group tolerance. Most importantly, broadly useful enantioselective catalysts for this emerging catalytic route for amine and *N*-heterocycle synthesis are targeted.

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

The authors declare no competing financial interest.

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