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Direct, Catalytic α-Alkylation of *N*-Heterocycles by Hydroaminoalkylation: Substrate Effects for Regiodivergent Product Formation

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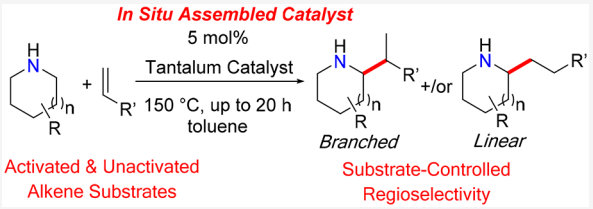
ABSTRACT: Saturated *N*-heterocycles are prevalent in pharmaceutical and agrochemical industries, yet remain challenging to catalytically alkylate. Most strategies for C−H activation of these challenging substrates use protected amines or high loadings of precious metal catalysts. We report an early transition-metal system for the broad, robust, and direct alkylation of unprotected amine heterocycles with simple alkenes. Short reaction times are achieved using an *in situ* generated tantalum catalyst that avoids the use of bases, excess substrate, or additives. In most cases, this catalyst system is selective for the branched reaction product, including examples of products that are generated with excellent diastereoselectivity. Alkene electronic properties can be exploited for substrate-modified regioselectivity to access the alternative linear amine alkylation product with a group 5 catalyst. This method allows for the facile isolation of unprotected *N*-heterocyclic products, as useful substrates for further reactivity.



INTRODUCTION

N-Heterocycles are privileged scaffolds in drug development, representing 59% of recently approved small-molecule treatments.[1] Saturated heterocycles such as piperidine, azepane, and tetrahydroquinoline are particularly prevalent yet remain some of the most challenging heterocycles to directly and selectively functionalize. The ability to selectively C−H functionalize *N*-heterocycles allows for the rapid generation of complex amine products from simple starting materials in one catalytic step. According to a recent minireview of catalytic C−H functionalization of heterocycles, less than 8% of reports disclose the ability to C−H functionalize saturated *N*-heterocycles and most demand the use of protected amine substrates.[2] Current literature to react saturated amine heterocycles is dominated by Csp^3−Csp^2 arylation[3−5] or Csp^3−Csp cyanation/alkynylation.[6,7] Photocatalytic cross-coupling can realize the α-C−H alkylation of protected saturated amines with activated electrophiles, such as aldehydes or alkyl halides,[8−11] or the stoichiometric α-alkylation of unprotected *N*-heterocycles can be achieved by the addition of organometallic nucleophiles to transiently generated imines.[12,13] These methods require activated alkylating agents that result in the generation of stoichiometric amounts of waste. An atom-economic alternative is to use alkenes as reagents for the catalytic alkylation of *N*-heterocycles by hydroaminoalkylation.

Various catalytic approaches exist to address the challenge of directly alkylating saturated *N*-heterocycles by hydroaminoalkylation (Figure 1). Recently developed photocatalytic strategies (Figure 1a) employ protected *N*-heterocycles in combination with Michael acceptors to generate the linear alkylation product.[14−19] Established late transition-metal hydroaminoalkylation strategies for protected heterocycle alkylation[20,21] benefit from good functional group tolerance and dominant regioselectivity for the linear reaction product with modest diastereoselectivity (Figure 1b).[21−32] Early transition-metal hydroaminoalkylation accesses the complementary branched α-alkylation product with a variety of secondary aryl and alkyl amines *without* the need for protecting/directing groups or cocatalysts/additives (Figure 1c).[33−36]

Group 5 hydroaminoalkylation uses free amines as substrates for addition to unactivated alkenes. To date, early transition-metal-catalyzed hydroaminoalkylation of unprotected *N*-heterocycles has remained largely unexplored. The only report focused on this transformation uses piperidine at high reaction temperatures (165 °C), with long reaction times (143 h) and high catalyst loadings (10 mol %).[37,38] This previous work required an isolated tantalum amidate precatalyst and an excess of unactivated alkene, such as 1-octene, to give only the branched reaction products. All products were protected and isolated as *N*-tosylates to facilitate isolation and characterization.[37,39] This latter protection step negates the potential

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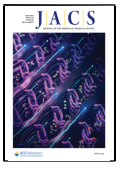

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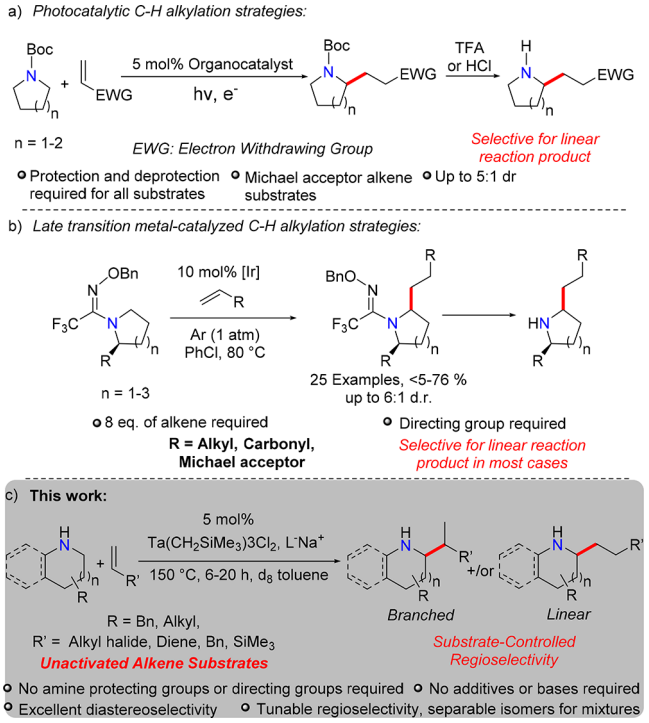


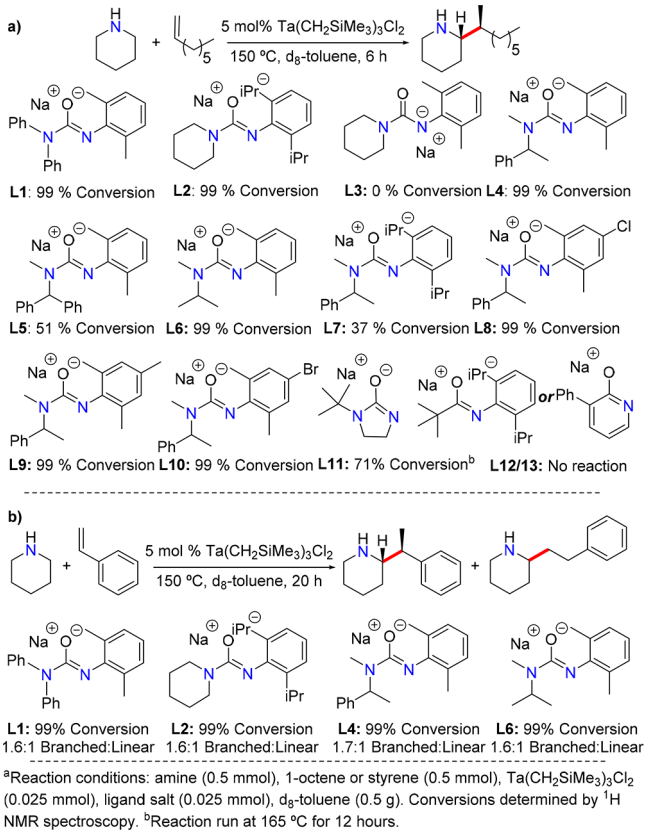
Figure 1. (a) Photocatalytic C−H alkylation of protected amines. (b) Late transition-metal-catalyzed hydroaminoalkylation of protected amines. (c) This work: A tantalum catalyst system for reactions of unprotected amines with unactivated alkene substrates.

advantage of preparing free amine products that are ready for further reactivity.[36,37,39−43] Some other early transition-metal catalysts have been reported for hydroaminoalkylation with specifically tetrahydroquinoline or tetrahydroisoquinoline.[39,44,45] However, due to the fused aryl ring, these are activated heterocycles and these same catalysts cannot be used with unactivated piperidines.[39,44,45]

Our group recently showed that highly active tantalum and titanium ureate hydroaminoalkylation catalysts can be prepared *in situ* for the efficient alkylation of both aryl and alkyl *N*-methylated secondary amines.[46−48] Although reactivity with *N*-heterocycles was not achieved, this earlier work showcased the tunable nature of ureate ligand salts to improve catalytic activity and enhance substrate scope. Here, we report a tantalum ureate catalyst for the rapid α-C−H alkylation of saturated *N*-heterocycles with activated and unactivated alkene coupling partners (Figure 1c). A simple protocol for *in situ* catalyst assembly is featured. Complete precatalyst characterization and catalytic evaluation is also presented. We show that this new catalyst system can be used at 5 mol % loading to give isolable, unprotected α-alkylated six- and seven-membered ring *N*-heterocycles. Investigations into alkene substrate scope revealed steric and electronic effects on regioisomeric control, with branched products being favored for unactivated alkenes, while activated styrene derivatives could be used for substrate-controlled linear regioisomer formation. This is the first early transition-metal-catalyst system that displays this shift from branched to linear products with these unactivated saturated *N*-heterocycles, providing insights that guide the development of further early transition-metal catalysts to access linear products.

RESULTS AND DISCUSSION

Ligand Design and Reaction Optimization. Initial reaction development efforts began by investigating the reaction between piperidine and 1-octene as benchmark substrates for *N*-heterocycle reactivity. Here, 5 mol % catalyst loading (equimolar amounts of Ta precursor and ligand salt) was used with a 1:1 mixture of the substrates at 150 °C for 6 h (Figure 2a). Both substrates are inexpensive, commercially



[a]Reaction conditions: amine (0.5 mmol), 1-octene or styrene (0.5 mmol), $Ta(CH_2SiMe_3)_3Cl_2$ (0.025 mmol), ligand salt (0.025 mmol), d_8-toluene (0.5 g). Conversions determined by ^{1}H NMR spectroscopy. [b]Reaction run at 165 °C for 12 hours.

Figure 2. Screening ureate ligand salts for hydroaminoalkylation with piperidine and (a) 1-octene and (b) styrene.

available, and represent challenging unactivated feedstocks. Attempts to achieve this transformation with the known simple tantalum complex $Ta(NMe_2)_5$[36,39,49] were unsuccessful under any reaction conditions. Using a known organometallic tantalum starting material, $Ta(CH_2SiMe_3)_3Cl_2$,[46,47] the benchmark reaction with piperidine over 24 h at 165 °C gave only 6% conversion, as determined by ^{1}H NMR spectroscopy.[50] None of the established amidate, pyridonate ligand salts (**L12**, **L13**) could be used for any reactivity with this challenging *N*-heterocycle substrate.[39,44,51] Only starting material remained by NMR spectroscopy after heating. However, when $Ta(CH_2SiMe_3)_3Cl_2$ was combined with various acyclic N,O-chelating ureate salts, seven very active catalyst combinations resulted (Figure 2; ligands **L1**, **L2**, **L4**, **L6**, **L8**−**L10**). This reaction did not generate any observable side products, as measured by NMR spectroscopy and GC−MS of the reaction mixture (See SI). These reactions achieved full conversion after only 6 h of reaction time at 150 °C.[52] The branched product was formed exclusively, in all cases, and a diagnostic doublet of the new methyl substituent was observed at 0.84 ppm in the ^{1}H NMR spectrum. All reactions also offered

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excellent diastereoselectivity for the major isomer indicated (>10:1).

Interestingly, the use of a cyclic ureate ligand salt, which has shown excellent reactivity with dialkyl amines,[51] was less effective when used with piperidine, even at longer reactions times of 12 h (**L11**). Known amidate and pyridonate ligands,[37,39,44,53,54] which have been used in hydroaminoalkylation catalysis with secondary amines (**L12** and **L13**), both showed no reaction with piperidine within 24 h. A comparison of results using the different acyclic ureate ligands showed that small structural changes resulted in unpredictable changes in reactivity (e.g., **L5** vs **L6**). Entries **L4** and **L8**−**L10** were tested to explore electronic effects on catalysis, but no changes could be noted with these varied *N*-aryl substituents.

Styrene is an activated alkene substrate that is typically more reactive than octene, but was previously unknown for addition to piperidine due to unwanted polymerization at the elevated temperatures required. Previous work from our group and others could not realize the alkylation of piperidine with styrene, regardless of reaction conditions. Here, we can use *in situ* generated Ta ureate mixtures to accomplish this challenging reaction. As shown in Figure 2b, entries **L1**, **L2**, **L4**, and **L6** show that the best catalysts for reactivity with 1-octene all display impressive reactivity with styrene, although longer reaction times of 20 h are required. Again, equivalent amounts of amine and styrene are used, and competing polymerization is not problematic. Further, these are the first examples of a group 5 hydroaminoalkylation catalyst that can access linear regioisomers with styrene substrate, as **L1**, **L2**, **L4**, and **L6** all generated significant amounts of this previously unobserved product. The diastereoselective formation of the branched product is retained with styrene substrates (*vide infra*).

To further develop and mechanistically explore this *N*-heterocycle reactivity, we continued experiments with the known ligand salt **L4**,[47] as the corresponding proteoligand can be easily synthesized and purified in large batches (up to 10 g) in excellent yield (86%) of recrystallized product. Further, the sodium salt of this ligand is soluble in toluene, facilitating stock solution preparation (*vide infra*) and *in situ* catalyst preparation and reaction setup. Although this ligand is chiral, previous work has shown that the incorporation of a remote stereocenter into the ligand is not useful for enantioselective hydroaminoalkylation.[47] Thus, all work here was done using the racemic ureate ligand.

Precatalyst Characterization. Isolation of Ta acyclic ureate complexes has proven challenging.[46,47] Here, the isolation, purification, and crystallographic characterization of the N,O-chelated complex resulting from the 1:1 reaction of ligand salt to $Ta(CH_2SiMe_3)_3Cl_2$ was achieved (Figure 3, **1**). This is the first example of a structurally characterized acyclic ureate-ligated Ta hydroaminoalkylation catalyst. Precatalyst **1** is monoligated with bond metrics that differ from those of a recently published group 5 N,O-chelated precatalyst with a cyclic ureate ligand.[51] For example, the Ta−N length in **1** of 2.155(3) Å is significantly longer than in the published cyclic ureate precatalyst (2.0694(15) Å). This longer Ta−N bond can be attributed to the bulky *N*-dimethylphenyl substituent in **1**. Overall, ureate ligands are bound much closer to the Ta metal center than related N,O-chelating amidate or pyridonate ligand scaffolds (e.g., Ta−N lengths of 2.447(3) and 2.307(1) Å, respectively),[53,55] indicating that ureate ligands are better able to stabilize negative charge and have a stronger

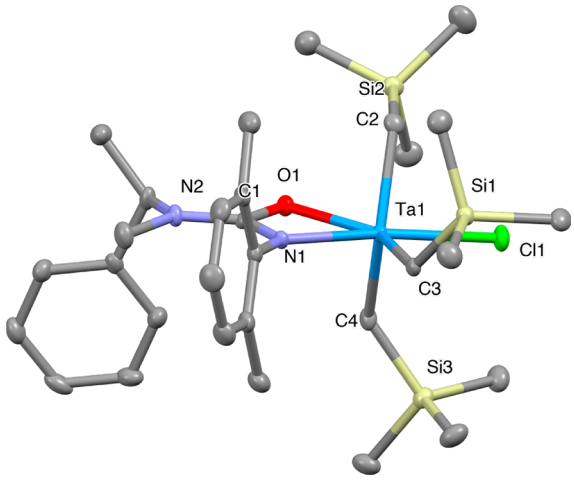

Figure 3. Solid-state molecular structure of precatalyst **1** determined by X-ray crystallography. Ellipsoids plotted at 50% probability, and H atoms omitted. Selected bond lengths (Å) and angles (deg): Ta−O1: 2.164(2), C1−N2: 1.338(4), C1−O1: 1.305(4), Ta−N1: 2.155(3), C1−N1: 1.341(4), O1−Ta−N1: 60.29(9), N1−Ta−C4:99.672.

electrostatic interaction with the electrophilic metal center. We propose that this bonding environment enhances ionic character in these complexes,[56] thereby increasing the polarized bonding in these early transition metal catalysts for enhanced hydroaminoalkylation reactivity.[57]

The catalytic activity of isolated precatalyst **1** was compared with *in situ* reactivity to ensure that the isolated material was representative of the catalyst system assembled *in situ*. Both experiments provided complete conversion to the branched product using optimized reaction conditions (20 h, 150 °C, 5 mol %). Furthermore, the ^{1}H NMR spectrum of isolated **1** matches that of the corresponding *in situ* generated mixture,[47] further confirming **1** is the dominant species prepared in solution. All further reactions in this work have been done using *in situ* precatalyst generation to simplify the synthetic protocol.

Substrate Scope and Reaction Mechanism. The substrate scope featured in this paper highlights not only functional group tolerance but also regioselectivity shifts that can be realized with electronically biased substrates. These results contrast with previous catalyst development work featuring Ta that largely gave branched products uniquely. This report that discloses a shift from branched product to linear product formation is complementary to a recent late transition-metal hydroaminoalkylation contribution that celebrates being able to access branched regioisomers in specific cases, rather than the more typical linear products.[32] A key difference between these complementary early and late transition metal advances in regiochemical control is the fact that here we show that early transition metal catalyst development can alter regiochemical outcomes, while late transition metal strategies focus on a *N*-protecting/directing group design to modify product ratios.

The lack of additives and excess substrates in early transition-metal-catalyzed hydroaminoalkylation allows for the isolation of the free N−H heterocyclic products directly (see SI), and *N*-tosylation for purification can be avoided. However, these unprotected secondary amine heterocyclic products are challenging to isolate and purify by column chromatography.[37,38] As a representative example, the hydro-

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J. Am. Chem. Soc. 2021, 143, 11243−11250

aminoalkylation of *p*-chlorostyrene with piperidine gave branched and linear regioisomers in 54 and 46% yield respectively (**22**/**23**, Table 2), as determined by ^{1}H NMR spectroscopy, using 1,3,5-trimethoxybenzene as an internal standard, and GC−MS. These compounds were then separated and purified by column chromatography in the reduced yields of 35 and 22%, respectively. Basified silica, alumina, or running manual vs automated columns did not improve the isolated yields. Also, it should be noted that diastereoenrichment may be observed upon purification on silica. In this case, the major diastereoisomer of the branched product (**22**) was obtained as one pure product (see SI). Furthermore, this same reaction was carried out on gram scale (over 1.5 g (25 mmol) of each starting material), to confirm that yields and product ratios are independent of reaction scale.

An alternative approach for optimizing yields features the use of a protecting group[37,38] installed after the reaction to ensure that products can be readily purified by chromatography. However, considering that unprotected *N*-heterocyclic products are directly amenable to further chemical modification, as has been shown in other hydroaminoalkylation/*N*-functionalization reaction sequences,[40,41,5] this protection step eliminates the synthetic opportunity afforded by early transition-metal-catalyzed hydroaminoalkylation. Thus, all the reported yields in Tables 1 and 2 are NMR yields. To confirm that unprotected products can indeed be isolated, column chromatography was used in each case to obtain pure materials for rigorous characterization. Relative stereochemistry was determined by comparing data from previous work[37] with 1D/2D NOESY experiments (see SI).

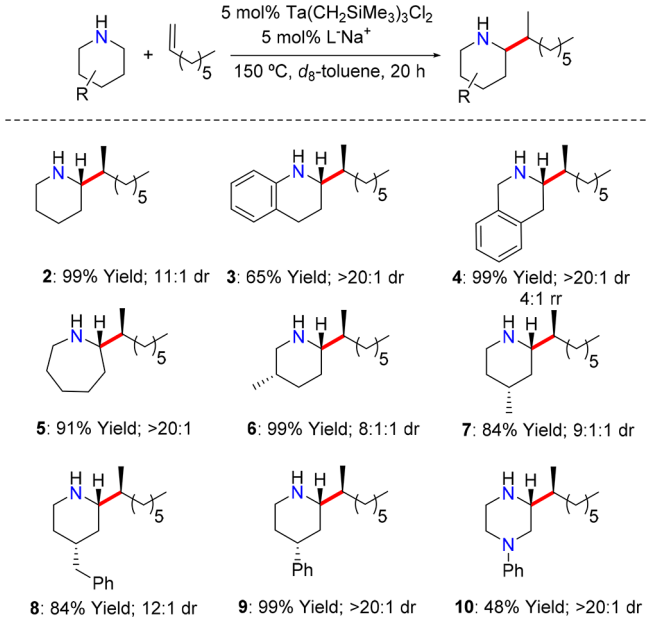
***N*-Heterocycle Scope.** With an easy to use catalyst system in hand, further exploration of the *N*-heterocycle substrate scope was undertaken. As shown in Table 1, *in situ* assembled compound **1** tolerates fused ring systems,[40,44] varied ring sizes, and substituted *N*-heterocycles to give exclusively branched product formation with unactivated alkene substrates. High yields are observed with most heterocycles (**2**−**9**), including a piperazine derivative that can undergo hydroaminoalkylation in moderate yield (**10**), as determined by ^{1}H NMR spectroscopy.

The tetrahydroisoquinoline substrate (compound **4**) shows good regioselectivity as determined by NMR spectroscopy, in which the isolated benzylic methylene group α to nitrogen at 3.97 ppm remains a singlet in the major product of the crude reaction mixture. There is no evidence of dialkylation. It is expected that the benzylic C−H bond of this *N*-heterocycle would be electronically favored for C−H activation; however, this site is sterically inhibited.

The preferred relative stereochemistry of the α,β-stereocenters in hydroaminoalkylation products is consistent across all heterocycles, including a seven-membered ring (Table 1, compound **5**). The excellent diastereoselectivity observed can be attributed to the metallacyclic intermediates of the proposed mechanism for early transition-metal-catalyzed hydroaminoalkylation (Figure 4).[37,58]

The catalytically active fused metallaaziridine (**C**) is formed via β-H abstraction. This aziridine undergoes facially selective alkene insertion such that the substituent of the alkene is oriented to the opposite face of the metallaaziridine ring **C** from the pyridyl ring.[37,44,59] Thus, alkene insertion into the fused metallacycle proceeds via transition-state **D** to give five-membered metallacycle **E** of defined relative stereochemistry. Then, another molecule of piperidine is involved in protonolysis, before a subsequent C−H activation releases the desired product and regenerates the metallaaziridine **C**.

Table 1. Amine Heterocycle Scope for C−H Alkylation[a]



[a]All amines were reacted and purified as free amine substrates. Reaction conditions: amine (1 mmol), alkene (1 mmol), Ta(CH$_2$SiMe$_3$)$_3$Cl$_2$ (0.05 mmol), ligand salt (**L4**, 0.05 mmol), d_8-toluene (0.6 g). NMR yields were determined using 1,3,5-trimethoxybenzene as an internal standard. Diastereoselectivity values are displayed as ratios, with the major diastereomer drawn and the ratio determined by GC−MS analysis.

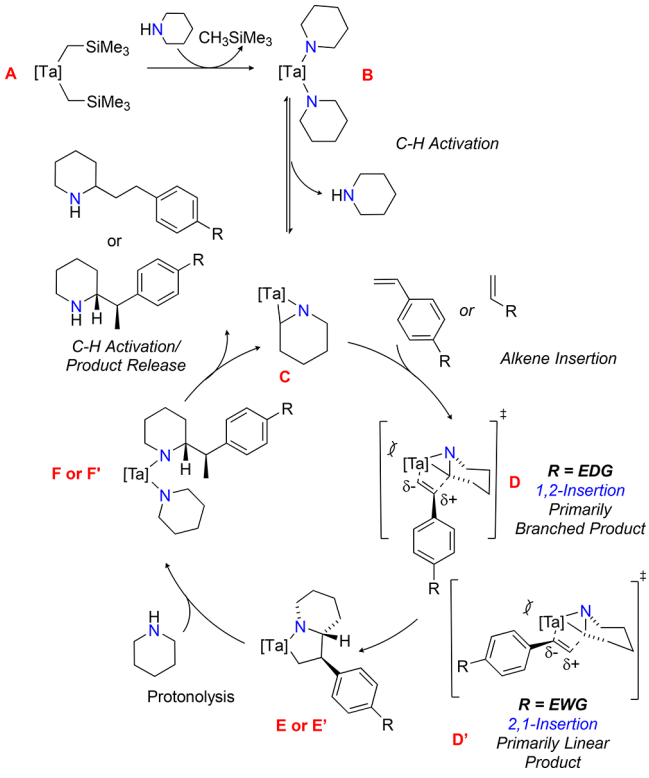


Figure 4. Proposed mechanism for hydroaminoalkylation with alkyltantalum precursors and saturated *N*-heterocycles.

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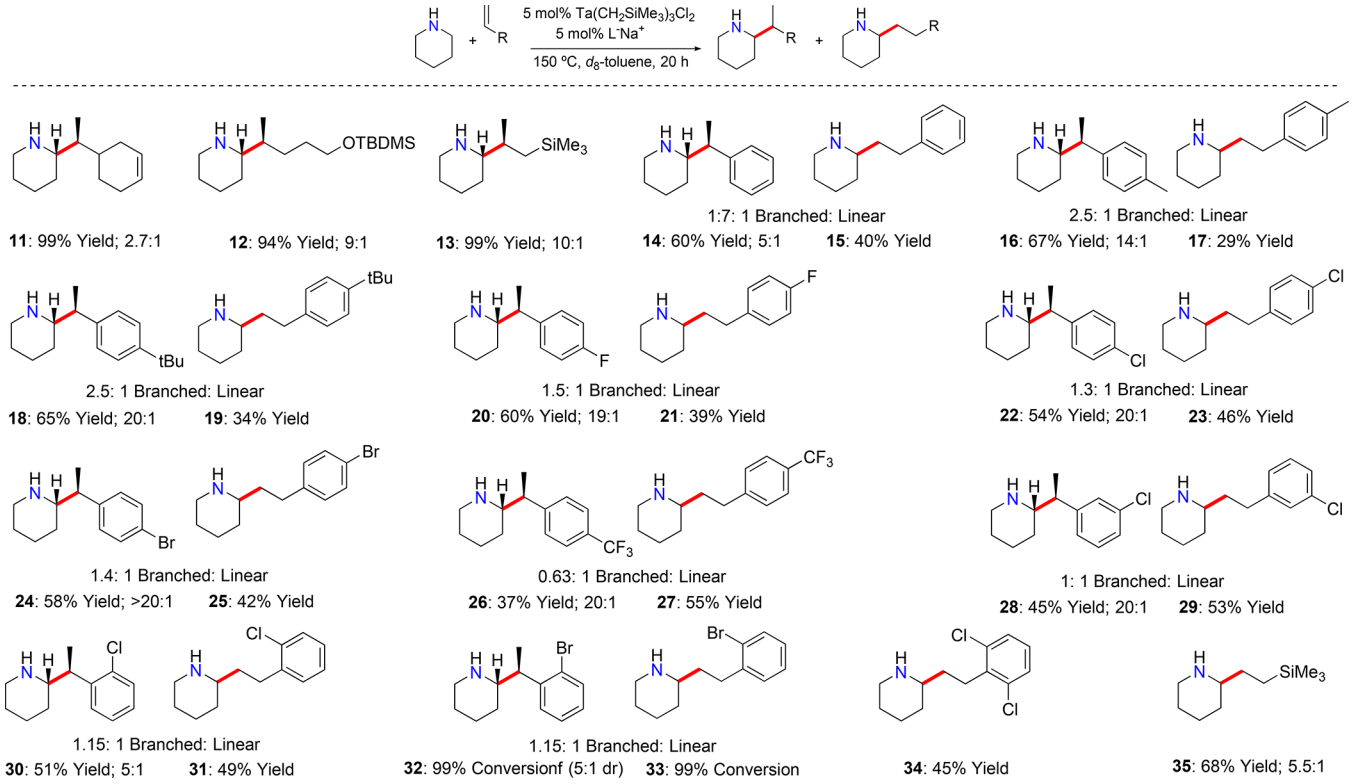
Table 2. Alkene Scope for Hydroaminoalkylation with Piperidine Using *N*-Heterocycles



[a]Reaction conditions: amine (1 mmol), alkene (1 mmol), $Ta(CH_2SiMe_3)_3Cl_2$ (0.05 mmol), ligand salt (**L4**, 0.05 mmol), d_8-toluene (0.6 g). NMR yields were determined with 1,3,5-trimethoxybenzene as an internal standard. Diastereoselectivity values are displayed as ratios, with the major diastereomer drawn and the ratio determined by GC−MS analysis.

The substituted piperazine in compound **10** highlights the potential for additional heteroatoms being compatible with this methodology, albeit with a lower yield (48%). Unfortunately, 4-methylpiperazine, unprotected piperazine, and morpholine show only unreacted starting materials remaining after heating. The incorporation of an aryl substituent, which reduces the nucleophilic character of the nitrogen of the piperazine, is important for promoting reactivity. Pyrrolidine was also not reactive with this catalyst, potentially due to aggregation/oligomerization.[60] This lack of reactivity contrasts with results using late transition-metal catalysts that prefer five-membered rings over piperidine-based systems.

Table 1 shows that this method can be used to set the relative stereochemistry of up to three positions in a single, diastereoselective catalytic step and the substituent at the 3- or 4-position impacts the stereochemical outcome of the reaction. While 3- or 4-substituted piperidine substrates were highly reactive, 2-methylpiperidine showed no reactivity, even after 20 h. This is consistent with the lack of dialkylation observed in all of these reactions. We attribute this observation to the challenging steric bulk that would need to be incorporated into metallacyclic species **C** and/or **D** or the protonolysis step from **E** to **F**.

Alkene Scope and Control of Regioselectivity. With various *N*-heterocycles in hand, next the alkene scope with piperidine was explored (Table 2). As expected, aliphatic alkenes (Table 2, compounds **11**−**13**) generate only branched product with unfunctionalized and functionalized terminal alkenes, and no reactivity with unactivated internal alkene substrates can be realized. This trend can be used to advantage to obtain complete selectivity for the terminal alkene of a diene substrate (**11**). A protected alcohol (**12**) resulted in the synthesis of branched product with excellent diastereoselectivity. Likewise, compound **13** illustrates reactivity with allyltrimethylsilane to give the branched product with excellent diastereoselectivity. The diastereoselective generation of the branched product (compound **15**, 11:1 dr as determined by GC−MS) can be rationalized by the mechanism that places the steric bulk away from the metal center and locates the preferred buildup of negative charge α to tantalum (Figure 4).

Next, an evaluation of reactivity with styrene derivatives was undertaken. As noted in Table 2, all styrenes gave significant amounts of both branched and linear regioisomers. By modifying the electronic features of the styrenes, substrate-modified regioselectivity is realized while maintaining excellent overall reactivity within 20 h (typically >90% combined yield). All reactions afforded product mixtures that were analyzed by quantitative NMR spectroscopy, using internal standard, and GC−MS was also used to confirm product ratios. As mentioned earlier, regioisomeric and sometimes diastereomeric products could be separated and isolated by column chromatography for complete characterization. As shown in entries **14** and **15**, the parent styrene gave the branched product over the linear product in a 1.7:1 ratio. This unsubstituted case was then compared to styrenes with a variety of aryl substituents.

Simple electron-donating alkyl substituents in the *para*-position resulted in the preferred formation of the branched product vs the linear product (2.5:1 for **16**:**17** and **18**:**19**). The branched product is formed with excellent diastereoselectivity

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in these cases. By employing electron-withdrawing substituents (**20**−**33**), including the inductively electron-withdrawing *ortho*-, *meta*-, and *para*-halides, and the trifluoromethyl group, the regioselectivity shifted to give more of the linear product (e.g., **26**:**27** gave a 0.63:1 branched:linear ratio). Excellent diastereoselectivity in the formation of the branched product remains (~20:1) except for the sterically demanding *ortho*-halide substituents. In these cases, the major diastereomer illustrated is formed in a 5:1 ratio. The impact of this electronic and steric effect was amplified in the dichlorosubstituted styrene (product **34**), whereby only the linear regioisomer was obtained. The compatibility of our tantalum catalyst with aryl halides could be used to advantage for posthydroaminoalkylation cross-coupling.

By taking advantage of these electronic effects upon regioselectivity, vinyltrimethylsilane (**35**), as shown previously,[43,61] furnishes the linear product selectively. This result can be rationalized by the silyl substituent stabilizing the buildup of negative charge on the α-carbon in the alkene insertion transition state (Figure 4, **D′**).[61−63]

Hammett Plot Analysis. With clear electronic trends observed in the regioselectivity of reactions with different styrene derivatives, a Hammett study was undertaken. The results of the reactions of piperidine with various *p*-substituted styrenes were compared. Figure 5 depicts the quantitative

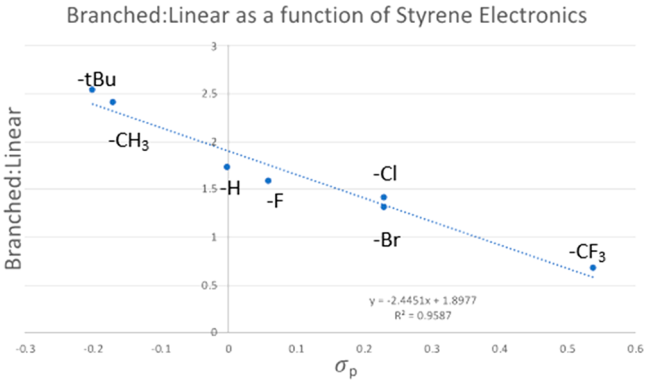

Figure 5. Branched:linear regioisomer ratios from Table 2 as plotted against Hammett parameters for hydroaminoalkylation reactions with a series of substituted styrene substrates.

dependence of branched:linear regioisomer ratios on the electronic effect of each styrene, as depicted using Hammett parameters for *p*-substituted substrates.[64,65] Overall, reactions using styrenes with electron-donating substituents resulted in more branched product, while styrenes with electron-withdrawing groups could be used to generate more of the linear regioisomer. However, this change in regioselectivity is dependent upon the use of challenging *N*-heterocycles, as the reaction of *N*-methylaniline with styrene with the same optimized catalyst affords mostly branched product (~9:1 B:L; see SI). The increased preference for multiple regioisomers with piperidine substrates is attributed to the bulky tantalaaziridine **C** intermediate amplifying the effects of varied alkene steric and electronic properties.

CONCLUSIONS

In summary, we have developed the first efficient catalyst for hydroaminoalkylation reactivity with a variety of unprotected *N*-heterocyclic substrates. Catalysis occurs with a loading of 5 mol % of a tantalum ureate catalyst, and full conversion can be realized in as little as 6 h depending on the chosen substrate. Isolated and *in situ* versions of our most active catalyst showed identical reactivity, allowing for the use of an easily assembled *in situ* catalyst system for the hydroaminoalkylation of *N*-heterocycles. The unprotected, selectively substituted *N*-heterocyclic products prepared here are suitable for direct modification. Variously substituted piperidines can be employed, and good diastereoselectivity was observed to set the relative stereochemistry of up to three stereocenters in a single catalytic transformation. The major diastereomer can be reliably predicted based on the mechanistic understanding of the key alkene insertion step. Also, by using this unique early transition metal catalyst, regiodivergent product formation could be observed with styrene substrates. Changes in regioselectivity allowed us to better understand the role of alkene electronic effects, as interpreted by a Hammett study, on the product distribution and reaction mechanism. This work shows that the direct C−H alkylation of unprotected *N*-heterocycles can be accomplished in an atom-economic fashion, using common alkene substrates as the alkylating agent. This early transition-metal-catalyzed approach, which avoids preactivated and/or protected substrates, offers new opportunities for assembling a diverse range of substituted *N*-heterocycles as precursors to more complex heterocyclic products.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c05498.

Experimental details and characterization data (PDF)

Accession Codes

CCDC 2086595 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare the following competing financial interest(s): The catalyst featured in this work has been patented: PCT/CA2018/050619.

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■ REFERENCES

(1) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257−10274.

(2) Kaur, M.; Van Humbeck, J. F. Recent Trends in Catalytic Sp^3 C-H Functionalization of Heterocycles. *Org. Biomol. Chem.* **2020**, *18*, 606−617.

(3) Baudoin, O. Transition Metal-Catalyzed Arylation of Unactivated C(Sp3)−H Bonds. *Chem. Soc. Rev.* **2011**, *40*, 4902−4911.

(4) He, C.; Gaunt, M. J. Ligand-Enabled Catalytic C-H Arylation of Aliphatic Amines by a Four-Membered-Ring Cyclopalladation Pathway. *Angew. Chem., Int. Ed.* **2015**, *54*, 15840−15844.

(5) Jain, P.; Verma, P.; Xia, G.; Yu, J.-Q. Enantioselective Amine α-Functionalization via Palladium-Catalysed C−H Arylation of Thioamides. *Nat. Chem.* **2017**, *9*, 140−144.

(6) Das, D.; Sun, A. X.; Seidel, D. Redox-Neutral Copper(II) Carboxylate Catalyzed α-Alkynylation of Amines. *Angew. Chem., Int. Ed.* **2013**, *52*, 3765−3769.

(7) Lennox, A. J. J.; Goes, S. L.; Webster, M. P.; Koolman, H. F.; Djuric, S. W.; Stahl, S. S. Electrochemical Aminoxyl-Mediated α-Cyanation of Secondary Piperidines for Pharmaceutical Building Block Diversification. *J. Am. Chem. Soc.* **2018**, *140*, 11227−11231.

(8) Shaw, M. H.; Shurtleff, V. W.; Terrett, J. A.; Cuthbertson, J. D.; MacMillan, D. W. C. Native Functionality in Triple Catalytic Cross-Coupling: Sp3 C-H Bonds as Latent Nucleophiles. *Science (Washington, DC, U. S.)* **2016**, *352*, 1304−1308.

(9) Le, C.; Liang, Y.; Evans, R. W.; Li, X.; MacMillan, D. W. C. Selective Sp3 C-H Alkylation via Polarity-Match-Based Cross-Coupling. *Nature* **2017**, *547*, 79−83.

(10) Zhou, W. J.; Cao, G. M.; Shen, G.; Zhu, X. Y.; Gui, Y. Y.; Ye, J. H.; Sun, L.; Liao, L. L.; Li, J.; Yu, D. G. Visible-Light-Driven Palladium-Catalyzed Radical Alkylation of C−H Bonds with Unactivated Alkyl Bromides. *Angew. Chem., Int. Ed.* **2017**, *56*, 15683−15687.

(11) Trowbridge, A.; Reich, D.; Gaunt, M. J. Multicomponent Synthesis of Tertiary Alkylamines by Photocatalytic Olefin-Hydroaminoalkylation. *Nature* **2018**, *561*, 522−527.

(12) Chen, W.; Ma, L.; Paul, A.; Seidel, D. Direct α-C-H Bond Functionalization of Unprotected Cyclic Amines. *Nat. Chem.* **2018**, *10*, 165−169.

(13) Paul, A.; Seidel, D. α-Functionalization of Cyclic Secondary Amines: Lewis Acid Promoted Addition of Organometallics to Transient Imines. *J. Am. Chem. Soc.* **2019**, *141*, 8778−8782.

(14) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. Visible-Light-Mediated Utilization of α-Aminoalkyl Radicals: Addition to Electron-Deficient Alkenes Using Photoredox Catalysts. *J. Am. Chem. Soc.* **2012**, *134*, 3338−3341.

(15) Dai, X.; Cheng, D.; Guan, B.; Mao, W.; Xu, X.; Li, X. The Coupling of Tertiary Amines with Acrylate Derivatives via Visible-Light Photoredox Catalysis. *J. Org. Chem.* **2014**, *79*, 7212−7219.

(16) Thullen, S. M.; Rovis, T. A Mild Hydroaminoalkylation of Conjugated Dienes Using a Unified Cobalt and Photoredox Catalytic System. *J. Am. Chem. Soc.* **2017**, *139*, 15504−15508.

(17) McManus, J. B.; Onuska, N. P. R.; Nicewicz, D. A. Generation and Alkylation of α-Carbamyl Radicals via Organic Photoredox Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 9056−9060.

(18) McManus, J. B.; Onuska, N. P. R.; Jeffreys, M. S.; Goodwin, N. C.; Nicewicz, D. A. Site-Selective C − H Alkylation of Piperazine Substrates via Organic Photoredox Catalysis. *Org. Lett.* **2020**, *22*, 679−683.

(19) Leng, L.; Fu, Y.; Liu, P.; Ready, J. M. Regioselective, Photocatalytic α-Functionalization of Amines. *J. Am. Chem. Soc.* **2020**, *142*, 11972−11977.

(20) Fukuyama, T.; Chatani, N.; Tatsumi, J.; Kakiuchi, F.; Murai, S. Ru3(CO)12-Catalyzed Site-Selective Carbonylation Reactions at a C-H Bond in Aza-Heterocycles. *J. Am. Chem. Soc.* **1998**, *120*, 11522−11523.

(21) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. $Ru_3(CO)_{12}$-Catalyzed Coupling Reaction of Sp3 C-H Bonds Adjacent to a Nitrogen Atom in Alkylamines with Alkenes. *J. Am. Chem. Soc.* **2001**, *123*, 10935−10941.

(22) Jun, C.-H. Chelation-Assisted Alkylation of Benzylamine Derivatives by Ru(0) Catalyst. *Chem. Commun.* **1998**, No. 13, 1405−1406.

(23) Pan, S.; Matsuo, Y.; Endo, K.; Shibata, T. Cationic Iridium-Catalyzed Enantioselective Activation of Secondary Sp3 C-H Bond Adjacent to Nitrogen Atom. *Tetrahedron* **2012**, *68*, 9009−9015.

(24) Mitchell, E. a.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W. Direct α-Functionalization of Saturated Cyclic Amines. *Chem. - Eur. J.* **2012**, *18*, 10092−10142.

(25) Smout, V.; Peschiulli, A.; Verbeeck, S.; Mitchell, E. A.; Herrebout, W.; Bultinck, P.; Vande Velde, C. M. L.; Berthelot, D.; Meerpoel, L.; Maes, B. U. W. Removal of the Pyridine Directing Group from α-Substituted N-(Pyridin-2-Yl)Piperidines Obtained via Directed Ru-Catalyzed Sp3C-H Functionalization. *J. Org. Chem.* **2013**, *78*, 9803−9814.

(26) Kulago, A. A.; Van Steijvoort, B. F.; Mitchell, E. A.; Meerpoel, L.; Maes, B. U. W. Directed Ruthenium-Catalyzed C(Sp3)-H α-Alkylation of Cyclic Amines Using Dioxolane-Protected Alkenones. *Adv. Synth. Catal.* **2014**, *356*, 1610−1618.

(27) Schinkel, M.; Wang, L.; Bielefeld, K.; Ackermann, L. Ruthenium(II)-Catalyzed $C(Sp^3)$−H α-Alkylation of Pyrrolidines. *Org. Lett.* **2014**, *16*, 1876−1879.

(28) Tran, A. T.; Yu, J.-Q. Practical Alkoxythiocarbonyl Auxiliaries for Iridium(I)-Catalyzed C-H Alkylation of Azacycles. *Angew. Chem., Int. Ed.* **2017**, *56*, 10530−10534.

(29) Schmitt, D. C.; Lee, J.; Dechert-Schmitt, A.-M. R.; Yamaguchi, E.; Krische, M. J. Ruthenium Catalyzed Hydroaminoalkylation of Isoprene via Transfer Hydrogenation: Byproduct-Free Prenylation of Hydantoins. *Chem. Commun.* **2013**, *49*, 6096−6098.

(30) Oda, S.; Sam, B.; Krische, M. J. Hydroaminomethylation beyond Carbonylation: Allene-Imine Reductive Coupling by Ruthenium-Catalyzed Transfer Hydrogenation. *Angew. Chem., Int. Ed.* **2015**, *54*, 8525−8528.

(31) Oda, S.; Franke, J.; Krische, M. J. Diene Hydroaminomethylation via Ruthenium-Catalyzed C−C Bond Forming Transfer Hydrogenation: Beyond Carbonylation. *Chem. Sci.* **2016**, *7*, 136−141.

(32) Verma, P.; Richter, J. M.; Chekshin, N.; Qiao, J. X.; Yu, J.-Q. Iridium(I)-Catalyzed C(Sp)−H Alkylation of Saturated Azacycles. *J. Am. Chem. Soc.* **2020**, *142*, 5117−5125.

(33) Roesky, P. W. Catalytic Hydroaminoalkylation. *Angew. Chem., Int. Ed.* **2009**, *48*, 4892−4894.

(34) Chong, E.; Garcia, P.; Schafer, L. Hydroaminoalkylation: Early-Transition-Metal-Catalyzed α-Alkylation of Amines. *Synthesis* **2014**, *46*, 2884−2896.

(35) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. Transition-Metal-Catalyzed C-H Alkylation Using Alkenes. *Chem. Rev.* **2017**, *117*, 9333−9403.

(36) Edwards, P. M.; Schafer, L. L. Early Transition Metal-Catalyzed C-H Alkylation: Hydroaminoalkylation for Csp3-Csp3 Bond Formation in the Synthesis of Selectively Substituted Amines. *Chem. Commun.* **2018**, *54*, 12543−12560.

https://doi.org/10.1021/jacs.1c05498
J. Am. Chem. Soc. 2021, 143, 11243−11250

(37) Payne, P. R.; Garcia, P.; Eisenberger, P.; Yim, J. C. H.; Schafer, L. L. Tantalum Catalyzed Hydroaminoalkylation for the Synthesis of α- and β-Substituted N-Heterocycles. *Org. Lett.* **2013**, *15*, 2182−2185.
(38) Braun, C.; Nieger, M.; Bräse, S.; Schafer, L. L. Planar-Chiral [2.2]Paracyclophane-Based Pyridonates as Ligands for Tantalum-Catalyzed Hydroaminoalkylation. *ChemCatChem* **2019**, *11*, 5264−5268.
(39) Eisenberger, P.; Ayinla, R. O.; Lauzon, J. M. P.; Schafer, L. L. Tantalum-Amidate Complexes for the Hydroaminoalkylation of Secondary Amines: Enhanced Substrate Scope and Enantioselective Chiral Amine Synthesis. *Angew. Chem., Int. Ed.* **2009**, *48*, 8361−8365.
(40) Zhang, Z.; Hamel, J. D.; Schafer, L. L. $TaMe_3Cl_2$-Catalyzed Intermolecular Hydroaminoalkylation: A Simple Complex for Enhanced Reactivity and Expanded Substrate Scope. *Chem. - Eur. J.* **2013**, *19*, 8751−8754.
(41) Lühning, L. H.; Strehl, J.; Schmidtmann, M.; Doye, S. Hydroaminoalkylation of Allylsilanes and a One-Pot Procedure for the Synthesis of 1,5-Benzoazasilepines. *Chem. - Eur. J.* **2017**, *23*, 4197−4202.
(42) Weers, M.; Lühning, L. H.; Lührs, V.; Brahms, C.; Doye, S. One-Pot Procedure for the Synthesis of 1,5-Benzodiazepines from N-Allyl-2-Bromoanilines. *Chem. - Eur. J.* **2017**, *23*, 1237−1240.
(43) Koperniku, A.; Foth, P. J.; Sammis, G. M.; Schafer, L. L. Zirconium Hydroaminoalkylation. An Alternative Disconnection for the Catalytic Synthesis of α-Arylated Primary Amines. *J. Am. Chem. Soc.* **2019**, *141*, 18944−18948.
(44) Chong, E.; Brandt, J. W.; Schafer, L. L. 2-Pyridonate Tantalum Complexes for the Intermolecular Hydroaminoalkylation of Sterically Demanding Alkenes. *J. Am. Chem. Soc.* **2014**, *136*, 10898−10901.
(45) Manßen, M.; Schafer, L. L. Titanium Catalysis for the Synthesis of Fine Chemicals-Development and Trends. *Chem. Soc. Rev.* **2020**, *49*, 6947−6994.
(46) DiPucchio, R. C.; Roşca, S. C.; Schafer, L. L. Catalytic and Atom-Economic Csp^3−Csp^3 Bond Formation: Alkyl Tantalum Ureates for Hydroaminoalkylation. *Angew. Chem., Int. Ed.* **2018**, *57*, 3469−3472.
(47) DiPucchio, R. C.; Rosca, S. C.; Athavan, G.; Schafer, L. L. Exploiting Natural Complexity: Synthetic Terpenoid-Alkaloids by Regioselective and Diastereoselective Hydroaminoalkylation Catalysis. *ChemCatChem* **2019**, *11*, 3871−3876.
(48) Manßen, M.; Deng, D.; Zheng, C. H. M.; Dipucchio, R. C.; Chen, D.; Schafer, L. L. Ureate Titanium Catalysts for Hydroaminoalkylation: Using Ligand Design to Increase Reactivity and Utility. *ACS Catal.* **2021**, *11*, 4550−4560.
(49) Dörfler, J.; Doye, S. A Commercially Available Tantalum Catalyst for the Highly Regioselective Intermolecular Hydroaminoalkylation of Styrenes. *Eur. J. Org. Chem.* **2014**, *2014*, 2790−2797.
(50) See SI for details. NMR conversions were determined by integrating the peak at 2.96 ppm corresponding to one H of the CH_2 α to the N in the hydroaminoalkylation product as compared with a disappearing piperidene peak at 2.63 ppm.
(51) Daneshmand, P.; Roşca, S. C.; Dalhoff, R.; Yin, K.; DiPucchio, R. C.; Ivanovich, R. A.; Polat, D. E.; Beauchemin, A. M.; Schafer, L. L. A Cyclic Ureate Ta Catalyst for Preferential Hydroaminoalkylation with Aliphatic Amines. Mechanistic Insights into Substrate Controlled Reactivity. *J. Am. Chem. Soc.* **2020**, *142*, 15740−15750.
(52) Conversion refers to formed amine product as observed by ^1H NMR spectroscopy in relation to unreacted piperidine starting material.
(53) Brandt, J. W.; Chong, E.; Schafer, L. L. Ligand Effects and Kinetic Investigations of Sterically Accessible 2-Pyridonate Tantalum Complexes for Hydroaminoalkylation. *ACS Catal.* **2017**, *7*, 6323−6330.
(54) Edwards, P. M.; Schafer, L. L. In Situ Generation of a Regio- and Diastereoselective Hydroaminoalkylation Catalyst Using Commercially Available Starting Materials. *Org. Lett.* **2017**, *19*, 5720−5723.
(55) Lauzon, J. M.; Eisenberger, P.; Roşca, S. C.; Schafer, L. L. Amidate Complexes of Tantalum and Niobium for the Hydroaminoalkylation of Unactivated Alkenes. *ACS Catal.* **2017**, *7*, 5921−5931.
(56) Leitch, D. C.; Platel, R. H.; Schafer, L. L. Mechanistic Elucidation of Intramolecular Aminoalkene Hydroamination Catalyzed by a Tethered Bis(Ureate) Complex: Evidence for Proton-Assisted C-N Bond Formation at Zirconium. *J. Am. Chem. Soc.* **2011**, *133*, 15453−15463.
(57) Nazemi, A.; Cundari, T. R. Importance of Nitrogen-Hydrogen Bond p Ka in the Catalytic Coupling of Alkenes and Amines by Amidate Tantalum Complexes: A Computational Study. *J. Phys. Chem. A* **2019**, *123*, 8595−8606.
(58) Gilmour, D. J.; Lauzon, J. M. P.; Clot, E.; Schafer, L. L. Ta-Catalyzed Hydroaminoalkylation of Alkenes: Insights into Ligand-Modified Reactivity Using DFT. *Organometallics* **2018**, *37*, 4387−4394.
(59) Lauzon, J. M. P.; Schafer, L. L. Tantallaaziridines: From Synthesis to Catalytic Applications. *Dalt. Trans.* **2012**, *41*, 11539.
(60) Chen, T. Y.; Tsutsumi, R.; Montgomery, T. P.; Volchkov, I.; Krische, M. J. Ruthenium-Catalyzed C-C Coupling of Amino Alcohols with Dienes via Transfer Hydrogenation: Redox-Triggered Imine Addition and Related Hydroaminoalkylations. *J. Am. Chem. Soc.* **2015**, *137*, 1798−1801.
(61) Garcia, P.; Lau, Y. Y.; Perry, M. R.; Schafer, L. L. Phosphoramidate Tantalum Complexes for Room-Temperature C-H Functionalization: Hydroaminoalkylation Catalysis. *Angew. Chem., Int. Ed.* **2013**, *52*, 9144−9148.
(62) Liu, F.; Luo, G.; Hou, Z.; Luo, Y. Mechanistic Insights into Scandium-Catalyzed Hydroaminoalkylation of Olefins with Amines: Origin of Regioselectivity and Charge-Based Prediction Model. *Organometallics* **2017**, *36*, 1557−1565.
(63) Dörfler, J.; Preuß, T.; Schischko, A.; Schmidtmann, M.; Doye, S. A 2,6-Bis(Phenylamino)Pyridinato Titanium Catalyst for the Highly Regioselective Hydroaminoalkylation of Styrenes and 1,3-Butadienes. *Angew. Chem., Int. Ed.* **2014**, *53*, 7918−7922.
(64) Hansch, C.; Leo, A.; Taft, R. W. A Survey of Hammett Substituent Constants and Resonance and Field Parameters. *Chem. Rev.* **1991**, *91*, 165−195.
(65) Coote, M. L.; Davis, T. P. Propagation Kinetics of Para-Substituted Styrenes: A Test of the Applicability of the Hammett Relationship to Free-Radical Polymerization. *Macromolecules* **1999**, *32*, 4290−4298.

https://doi.org/10.1021/jacs.1c05498
J. Am. Chem. Soc. 2021, 143, 11243−11250