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# $TaMe_3Cl_2$-Catalyzed Intermolecular Hydroaminoalkylation: A Simple Complex for Enhanced Reactivity and Expanded Substrate Scope

**Zhengxing Zhang, Jean-Denys Hamel, and Laurel L. Schafer*[a]**

Amines are common naturally occurring compounds that attract the interest of organic chemists and medical scientists due to their prevalence in biologically active molecules. Atom-economic synthetic routes for the efficient preparation of amines rely on the development of catalytic reactions, such as hydroamination[1] and more recently hydroaminoalkylation.[2]

Hydroaminoalkylation, or the α-alkylation of amines, is an emerging catalytic C–H functionalization technology for the addition of an $sp^3$-hybridized C–H bond α to nitrogen across the C=C double bond of an alkene. Late transition metals, such as Ir and Ru, can be used in combination with pyridyl-substituted amines to realize chelation-assisted $sp^3$ C–H bond functionalization with alkenes.[3] However, early-transition-metal-catalyzed hydroaminoalkylation is particularly attractive because unprotected amines can be used as substrates.

Recent achievements in hydroaminoalkylation catalyst development include the use of Group 4[4] and Group 5[5] metal complexes, in which Group 5 complexes have shown particular promise for the intermolecular variant of this reaction with excellent regioselectivity for the branched product and even high enantioselectivity with selected substrates.[5f,g] With these promising reactivity trends identified, current efforts are focused on improving the performance of these catalysts to address limitations of high reaction temperatures (often over 130 °C), long reaction times (up to 60 h), and significant substrate-scope limitations. Herein, we show that the simple $TaMe_3Cl_2$[6] organometallic complex, a common Ta starting material, can be used to realize such transformations at 110 °C. Most importantly, a broad range of terminal and even internal alkenes can undergo hydroaminoalkylation with both alkylaryl- and dialkylamines to give β-substituted secondary amine products in high yields. Furthermore, we show that this catalyst system can be incorporated into one-pot synthetic transformations, as illustrated in the efficient catalytic preparation of 3-methyl-*N*-phenylindoline.

[a] Dr. Z. Zhang, J.-D. Hamel, Prof. Dr. L. L. Schafer
Department of Chemistry
University of British Columbia
2036 Main Mall, Institution
Vancouver, BC, V6T 1Z1 (Canada)
E-mail: schafer@chem.ubc.ca

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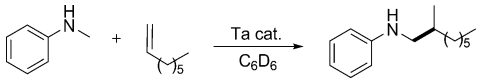
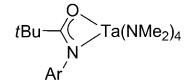
Doye and co-workers showed that the replacement of the amido ligands of $Ti(NMe_2)_4$ with the benzyl ligands of $Ti(CH_2Ph)_4$ both enhanced hydroaminoalkylation reactivity and eliminated the formation of amine by-products derived from the ligand itself.[4c,7]

Furthermore, Doye and co-workers have shown that by introducing an auxiliary ligand, catalysts with enhanced substrate scope and alternative regioselectivities can be accessed.[4d,g] Inspired by their achievements by using Ti alkyls and Herzon and Hartwig's demonstration that chloride complexes of Ta (e.g., $[Cl_3Ta(NMePh)_2]_2$) realize reactivity with temperatures as low as 90 °C with selected substrates (Table 1, entry 5),[5b] we undertook the investigation of the common $TaMe_3Cl_2$ complex as a catalyst for hydroaminoalkylation. By using this precatalyst, methane gas is eliminated to generate the requisite tantalaziridine reactive intermediate (Figure 1).[8] Thus, the use of readily prepared $TaMe_3Cl_2$ for hydroaminoalkylation provides access to reactions with high yield at reduced reaction temperatures, reasonable reaction times, and with a significantly expanded substrate scope, while avoiding amine by-product formation.

Table 1. Reactivity comparison of Group 4 and Group 4 hydroaminoalkylation precatalysts.




| Entry | Catalyst | Conditions | Conv. [%] |
|---|---|---|---|
| 1 | $Ti(NMe_2)_4$ | 10 mol %, 160 °C, 96 h | 32[a,4c] |
| 2 | $TiBn_4$ | 10 mol %, 160 °C, 96 h | 77[a,4c] |
| 3 | $Ind_2TiMe_2$ | 2 mol %, 105 °C, 24 h | 90[a,4d] |
| 4 | $Ta(NMe_2)_5$ | 5 mol %, 110 °C | n.r. |
| 5 | $[Cl_3Ta(NMePh)_2]_2$ | 2 mol %, 90 °C, 24 h | 72[a,5b] |
| 6 |  | 5 mol %, 110 °C, 63 h | 96[a,5c] |
| 7 | $TaMe_3Cl_2$ | 10 mol %, 110 °C, 30 h | 91 |

[a] Reported yields; n.r. = no reaction.

For a common screening reaction of *N*-methylaniline with 1-octene, it is shown in Table 1 that by changing from amido ligands on the Ti precatalyst to benzyl ligands, improved conversions were achieved, although reaction temperatures of 160 °C were required (Table 1, entries 1 and 2).[4b,c] Further tuning of the reactivity of the metal center using an auxiliary ligand, for example using $Ind_2TiMe_2$, results in en-

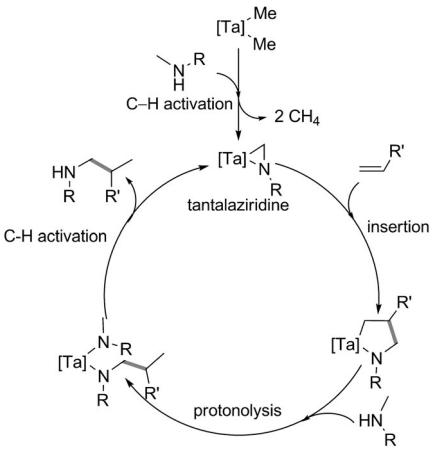
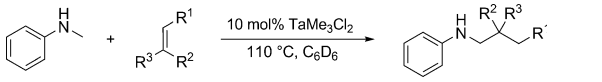


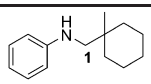
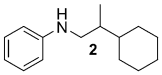
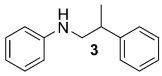
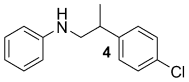
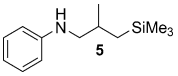
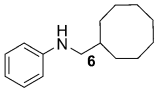
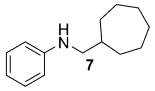
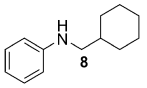
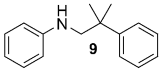
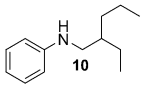
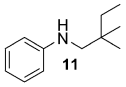

Figure 1. Simplified proposed catalytic cycle showing methane elimination.

hanced conversions and short reaction times (Table 1, entry 3).[4d] Notably, $Ind_2TiMe_2$ performed well on this particular substrate combination, but did suffer from a limited substrate scope. For example, the reaction of *p*-methoxy-*N*-methylaniline and styrene gave less than 5% yield.[4d] In a shift to Group 5 catalysts for this transformation, the commercially available $Ta(NMe_2)_5$ gave no product at modest reaction temperatures of 110°C (Table 1, entry 4). The effect of the aforementioned electron-withdrawing chloride substituent is shown in entry 5, in which good reactivity was observed at only 90°C.[5b] Our previously reported Ta amidate precatalyst $[(2,6\text{-}i\text{Pr}_2C_6H_3NC(t\text{Bu})O)Ta(NMe_2)_4]$ can realize this transformation with extended reaction times at 110°C (Table 1, entry 6).[5c] The reactivity of $TaMe_3Cl_2$ is comparable to the aforementioned Ta amidate complex (Table 1, entry 7) and a catalyst loading of 10 mol% resulted in near complete conversion in 30 h. Most importantly, further investigation revealed a dramatically improved substrate scope for the synthesis of α-alkylated unprotected secondary alkylaryl- and dialkylamines with this precatalyst.

By using simple $TaMe_3Cl_2$, we investigated the substrate scope of this system with *N*-methylaniline as the limiting reagent and two equivalents of various alkenes. To our delight, the reaction of *N*-methylaniline and methylenecyclohexane was completed in only 15 h at 110°C (Table 2, entry 1). This reaction generates a quaternary center β to N in one simple catalytic transformation. In comparison, previous reports for this substrate combination required reaction temperatures of 140°C for 48 h to give the desired product in 72% yield.[5g] As shown for entry 2 (Table 2), the more sterically demanding terminal alkene, vinylcyclohexane, underwent hydroaminoalkylation smoothly to give the corresponding branched product in good yield. Notably, the results presented herein are consistent with previous reports for Group 5 catalyzed hydroaminoalkylation catalysis, in which regioselective alkene insertion results in the formation of the branched product (Figure 1).[5] Styrene substrates also worked very well in spite of its propensity for polymerization in the presence of such Lewis acidic catalysts (Table 2, entry 3). Implication of *p*-chlorostyrene gave products in good yield with slightly longer reaction times (Table 2, entry 4). Allylsilane is an effective reaction partner, and this substituent pattern could allow further functional-group manipulation (Table 2, entry 5). Although extended times are required, the reaction at the internal double bond of cyclooctene occurred at 110°C in 73% yield (Table 2, entry 6). The ring strain of the cycloalkene starting material dramatically affected hydroaminoalkylation reactivity, as shown in entries 7 and 8 (Table 2), in which cycloheptene is much more reactive than cyclohexene. Elevated reaction temperatures were required for cyclohexene to give a product in moderate yield. To the best of our knowledge, this is the first report of cyclohexene as a possible substrate for hydroaminoalkylation. α-Methylstyrene has been previously reported to be unreactive with Group 5 metal–binaphtholate complexes.[5g] Using $TaMe_3Cl_2$, α-methylstyrene reacted with *N*-methylaniline to give the corresponding hydroaminoalky-

Table 2. Alkene substrate scope by using $TaMe_3Cl_2$ as a precatalyst.



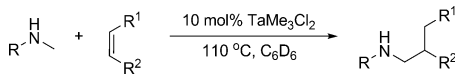

| Entry | Alkene | Product | *t* [h] | Yield [%][a] |
|---|---|---|---|---|
| 1 |  |  | 15 | 88 |
| 2 |  |  | 30 | 81 |
| 3 |  |  | 31 | 93 |
| 4 |  |  | 35 | 84 |
| 5 |  |  | 20 | 81 |
| 6 |  |  | 102 | 73 |
| 7 |  |  | 30 | 83 |
| 8[b] |  |  | 88 | 47 |
| 9[c] |  |  | 144 | 61 |
| 10[b] |  |  | 65 | 36 |
| 11[b] |  |  | 72 | 16 |

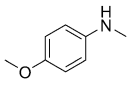
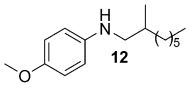
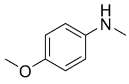
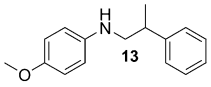
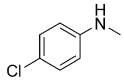
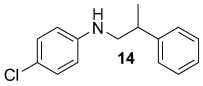
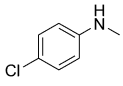
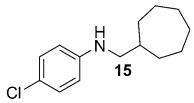
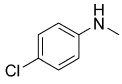
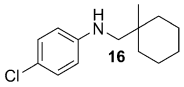
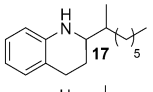
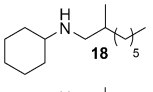
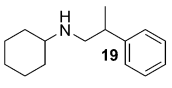
[a] Isolated yields. [b] $T = 145$°C. [c] $T = 130$°C.

lation product in moderate yield at 130 °C with extended reaction times (Table 2, entry 9). Impressively, the linear unstrained internal alkene *cis*-3-hexene could also be used with our catalyst, although a higher temperature and longer reaction time were required. This is the first time that such linear internal alkenes have been reported to be viable substrates for hydroaminoalkylation reactivity (Table 2, entry 10). To our delight, even the sterically demanding internal alkene 2-methyl-2-butene was observed to undergo regioselective hydroaminoalkylation with *N*-methylaniline to give the desired product, albeit in low isolated yield (Table 2, entry 11).

The observed broad alkene substrate scope encouraged us to further evaluate viable amine substrates that can be used with this catalyst system (Table 3). The reaction of *p*-methoxy-*N*-methylaniline with 1-octene shows similar reactivity

Table 3. Amine substrate scope by using $TaMe_3Cl_2$ as a precatalyst.

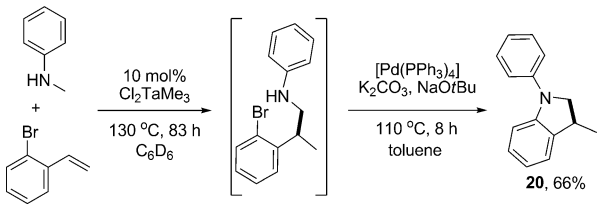



| Entry | Amine | Alkene | Product | $t$ [h] | Yield [%][a] |
|---|---|---|---|---|---|
| 1 |  |  |  **12** | 30 | 74 |
| 2 |  |  |  **13** | 86 | 69 |
| 3[b] |  |  |  **14** | 46 | 89 |
| 4 |  |  |  **15** | 39 | 76 |
| 5 |  |  |  **16** | 6 | 86 |
| 6 |  |  |  **17** | 46 | 71 |
| 7 |  |  |  **18** | 37 | 84[c] |
| 8 |  |  |  **19** | 65 | 85[c] |

[a] Isolated yields. [b] $T = 100$ °C. [c] Isolated as the tosyl-protected amine.

to that of *N*-methylaniline, while the reaction with styrene as a reaction partner is much slower (Entries 1 and 2). However, *p*-chloro-*N*-methylaniline showed improved reactivity to that of *N*-methylaniline when reacted with styrene or cycloheptene (Entries 3 and 4). The reaction of *p*-chloro-*N*-methylaniline with methylenecyclohexane finished in only 6 h at 110 °C (Entry 5). Ethyl- rather than methyl-substituted aniline derivatives were unreactive under these reaction conditions. However, as shown in entry 6, the heterocyclic secondary amine tetrahydroquinoline shows good reactivity at 110 °C, although piperidines have not been successful substrates, even when high reaction temperatures and long reactions times are used. Previously, dialkylamines have been reported to be more challenging substrates than arylalkylamines for hydroaminoalkylation.[5b] However, $TaMe_3Cl_2$ can be used with cyclohexylmethylamine at only 110 °C to give both alkyl- or aryl-substituted products in good yields (Entries 7 and 8).

For Group 5 precatalysts reported to date, only modest functional-group incorporation at the olefin has been explored.[5] Halogen-substituted styrene derivatives are particularly attractive reaction partners, because they allow subsequent transformations through palladium-catalyzed coupling protocols. Accordingly, we envisaged a facile, tandem reaction to efficiently prepare indoline derivatives based on sequential Ta-catalyzed hydroaminoalkylation and Pd-catalyzed Buchwald–Hartwig coupling in one pot. Biorelevant targets, such as indolines,[9] are important heterocycles in the pharmaceutical and agrochemical industries, and efficient approaches for their syntheses are highly desirable. Herein, we showed that by using the atom-economic $TaMe_3Cl_2$ precatalyst, which eliminates amine by-product formation, the clean formation of the hydroaminoalkylation product of *N*-methylaniline and *o*-bromostyrene was achieved. This intermediate can then undergo palladium-catalyzed intramolecular amination to give 3-methyl-*N*-phenylindoline in one pot in 66 % overall yield from commercially available precursors (Scheme 1). This compares favorably with the reported synthesis of **20** by reduction of an indoline-2-thione intermedi-




Scheme 1. One-pot synthesis of 3-methyl-*N*-phenylindoline: one-pot $TaMe_3Cl_2$-catalyzed hydroaminoalkylation of α-bromostyrene and palladium-catalyzed cyclization.

ate in 37 % yield.[10] This synthetic approach demonstrates the compatibility of $d^0$ Ta catalysts with late-transition-metal redox-active catalysts for the development of one-pot sequential syntheses that take advantage of the atom-economic hydroaminoalkylation reaction.

In conclusion, we have shown that $TaMe_3Cl_2$ is a readily accessible and highly efficient hydroaminoalkylation catalyst that can be used with a broad range of amine and alkene substrates, including some known challenging starting materials, such as styrene, disubstituted terminal alkenes, internal unstrained alkenes, and dialkylamines. To further distinguish this catalyst system from previously reported tantalum–amido complexes, $TaMe_3Cl_2$ did not generate any amine by-

products during the reaction due to the release of $CH_4$ upon precatalyst activation. This catalyst system can be used to efficiently install quaternary-carbon centers β to N and is amenable to the development of one-pot reaction protocols, as was illustrated in the efficient preparation of 3-methyl-*N*-phenylindoline. Future work focuses on mechanistic investigations to guide the development of auxiliary ligands to realize asymmetric catalysis with Group 5 alkyl precatalysts.

## Experimental Section

**General procedure for $TaMe_3Cl_2$-catalyzed hydroaminoalkylation of alkenes**: In a nitrogen-filled glove box, $TaMe_3Cl_2$ (10 mol%), amine (1 equiv), and olefin (1 equiv) were put into three small vials. $TaMe_3Cl_2$ was dissolved in $C_6D_6$ (0.50 mL). The amine and olefin were mixed and added to the $TaMe_3Cl_2$ solution. The solution was transferred to an NMR tube equipped with a Teflon cap, and the vials were rinsed with $C_6D_6$ (total volume 0.50 mL), in three rinses. The NMR tube was closed, shaken, and the $^1$H NMR spectrum was recorded. The NMR tube was placed in a preheated oil bath at the indicated temperature for the given time. After confirmation of conversion by $^1$H NMR spectroscopy, the crude reaction mixture was directly loaded onto a silica-gel column and eluted by using a mixture of hexanes/EtOAc or hexanes/$CH_2Cl_2$.

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**Keywords:** alkylation · atom-economic catalysis · C–H functionalization · hydroaminoalkylation · tantalum

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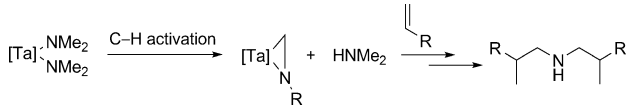
[7] Hydroaminoalkylation reactions by using Group 4 and Group 5 metal–amido precatalysts can require laborious product purification protocols because of the contaminating dialkylamine by-products resulting from hydroaminoalkylation of the dimethyl amine generated upon precatalyst activation; see Ref. [3e–g, 4c].

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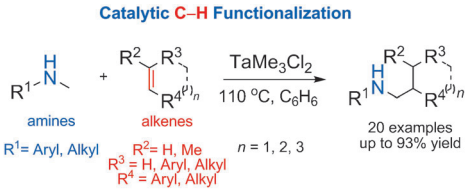


**Tantalizingly simple**: The common organometallic starting material $TaMe_3Cl_2$ can be used for the catalytic C–H functionalization reaction, hydroaminoalkylation. The substrate scope for this readily accessed compound includes unactivated terminal and internal alkenes, styrene derivatives, and both alkylaryl- and dialkyl secondary amines (see scheme).

**Alkylation**

*Z. Zhang, J.-D. Hamel, L. L. Schafer** ..... ▮▮▮▮–▮▮▮▮

**$TaMe_3Cl_2$-Catalyzed Intermolecular Hydroaminoalkylation: A Simple Complex for Enhanced Reactivity and Expanded Substrate Scope**