Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX-XXX

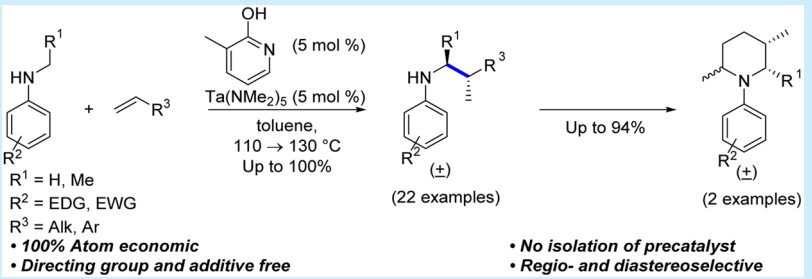
pubs.acs.org/OrgLett

In Situ Generation of a Regio- and Diastereoselective Hydroaminoalkylation Catalyst Using Commercially Available Starting Materials

Peter M. Edwards and Laurel L. Schafer*

Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, British Columbia, Canada V6T 1Z1

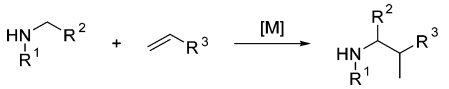
Supporting Information



ABSTRACT: The design of an easy to use catalyst system for the regio- and diastereoselective intermolecular hydroaminoalkylation of alkenes with secondary amines is reported. The method utilizes commercially available ligands and tantalum starting materials, and does not require the isolation of air and water sensitive organometallic complexes. The *in situ* prepared catalyst is active toward a variety of secondary amine substrates, including those with ethyl substituents which yield α- and β-alkylated amines as a single diastereomer. This catalytic transformation can be used to prepare amines containing functionality that promotes ring closure to achieve the diastereoselective synthesis of di- and trialkylated *N*-heterocycles.

Amines have a vast array of applications, from pharmaceuticals,[1] to agrochemicals,[2−4] and materials.[5−8] Consequently, catalytic methods for amine synthesis are an ongoing area of research. Significant effort has gone into the development of catalytic C−N bond forming reactions that utilize readily available alkene and alkyne feedstocks, including hydroamination or hydroformylation followed by reductive amination (hydroaminomethylation).[9−13] Notably, the synthesis of selectively substituted amines with alkenes can also be achieved through hydroaminoalkylation (Scheme 1).[14−20] This C−H alkylation reaction allows for the synthesis of α- and β-alkylated/arylated secondary amines. This catalytic method forms a C(sp^3)−C(sp^3) bond α to an amine by addition of a C−H bond across a C=C bond of activated and unactivated alkenes, while avoiding the use of protecting groups, photoredox catalysts, or exogenous oxidants. This reaction can be catalyzed by early transition metals, which are inexpensive, and the relevant starting materials are commercially available.[21−23]

Scheme 1. Regioselective Hydroaminoalkylation Reaction



Early transition metal catalyzed hydroaminoalkylation has the potential to be a powerful synthetic tool, and ongoing research efforts for this reaction aim to address the following challenges in catalyst development: laborious ligand syntheses,[14,17,18,24] handling of highly reactive metal precursors,[25,26] and use of isolated precatalysts (Figure 1). Here we show that these challenges can be resolved through the development of a catalyst system that can be assembled *in situ* from commercially available starting materials using traditional syringe techniques.

Our group has developed several rigorously characterized hydroaminoalkylation precatalysts (Figure 1), and the proligands **L1**, **L2**, **L3** required for their generation are shown in Figure 2.[27,14,26] These same proligands were tested for *in situ* generation of precatalysts, and the subsequent catalytic activity for the hydroaminoalkylation benchmark reaction of 1-octene with *N*-methylaniline is shown in Table 1. *In situ* catalyst preparation is achieved using a simple protonolysis reaction between Ta(NMe_2)$_5$ and the respective proligand at room temperature for 15 min.

The modest reaction temperature of 110 °C was selected to facilitate the use of toluene as solvent. As shown in entry 1, commercially available Ta(NMe_2)$_5$ alone proved to be a poor catalyst under these conditions; however, the addition of an *N*,*O*-chelating ligand drastically increased conversion (Table 1, entries 2−13). It is worth noting that the use of an *in situ* prepared catalyst is identical to employing the isolated precatalyst (Table 1, entries 2−3 and 4−5). The use of the amide **L1** increased conversion to 87% within 24 h, while both pyridones **L2** and **L3**

Received: July 14, 2017

DOI: 10.1021/acs.orglett.7b02149
Org. Lett. XXXX, XXX, XXX−XXX

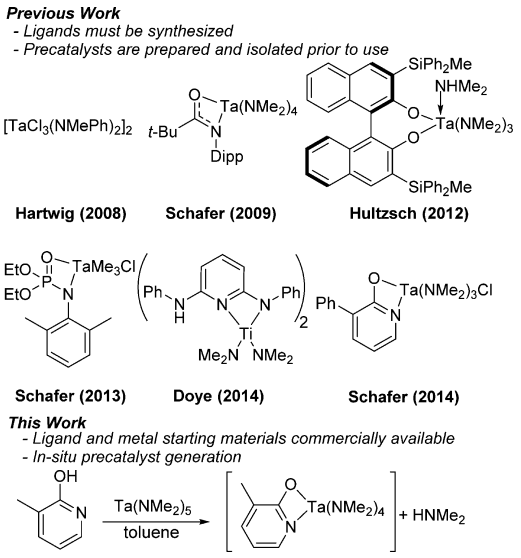


Figure 1. Comparison of *in situ* formed pyridonate catalyst with previously reported hydroaminoalkylation catalysts.

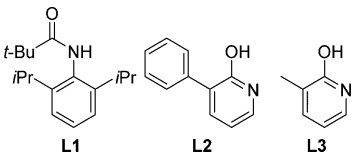
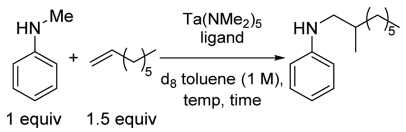


Figure 2. *N,O*-Proligands used for *in situ* catalyst synthesis.

Table 1. *In Situ* Catalyst Screening and Optimization[a]



entry	ligand	temp (°C)	time (h)	conv (%)[b]	yield (%)[c]
1	none	110	24	16	N/A
2	**L1**[d]	110	24	87	N/A
3	**L1**	110	24	87	N/A
4	**L2**[d]	110	24	100	N/A
5	**L2**	110	24	100	N/A
6	**L3**	110	24	100	95
7	**L3**	100	24	95	90
8	**L3**	90	24	26	21
9	**L3**	110	24[e]	41	35
10	**L3**	110	16	13	7
11	**L3**	110	16[f]	87	82
12	**L3**	110	16[f,g]	100	96
13	**L3**	110	16[h]	96	91

[a]Reaction performed in a J-Young tube with 5 mol % [Ta] and 5 mol % ligand unless stated otherwise. [b]Determined by ^{1}H NMR spectroscopy through relative integration of *ortho*-aniline peaks. [c]Isolated yield. [d]Isolated catalyst used. [e]2.5 mol % catalyst. [f]Ligand and [Ta] allowed to stir for 15 min prior to addition of substrates. [g]Reaction performed in a 20 mL vial with a PTFE cap. [h]Reaction performed on 1 g scale with 0.0825 M stock solution of catalyst in a three-necked flask.

(Table 1, entry 6) led to full conversion. Ligands **L2** and **L3** also benefit from selectively forming the monoligated complex,[28] which allows for the *in situ* formation of the catalytic species while avoiding less active bis-ligated complexes.[14] Given that **L3** is commercially available while **L1** and **L2** must be synthesized, **L3** was selected for further development.

A reduction in the reaction temperature from 110 to 90 °C resulted in a significantly reduced yield (Table 1, entry 8). Likewise a reduction in the catalyst loading to only 2.5 mol % resulted in a significant reduction in yield within the desired 24 h time frame of the experiment (Table 1, entry 9). It was also discovered that allowing the ligand and $Ta(NMe_2)_5$ to react prior to addition of the substrates is important for reducing the reaction time, increasing the 16 h conversion from 13% (Table 1, entry 10) to 87% (Table 1, entry 11). An additional benefit of **L3** is that it is soluble in toluene, allowing for the use of stock solutions of both proligand and $Ta(NMe_2)_5$ and thus increasing the ease of reaction setup in either the glovebox or using routine syringe techniques. The proposed mechanism of this reaction is shown in Figure 3.

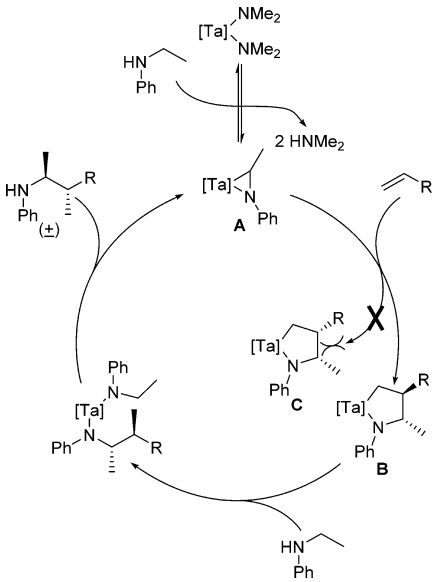
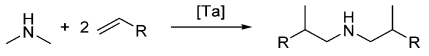


Figure 3. Proposed hydroaminoalkylation mechanism.

As shown in Figure 3, precatalyst activation to form **A** is accompanied by dimethylamine elimination. This dimethylamine can then become a substrate for the reaction, and thus a byproduct that is often observed is the product of the bis-alkylation of dimethylamine (Scheme 2).[29]

Scheme 2. Formation of Dimethylamine Byproduct



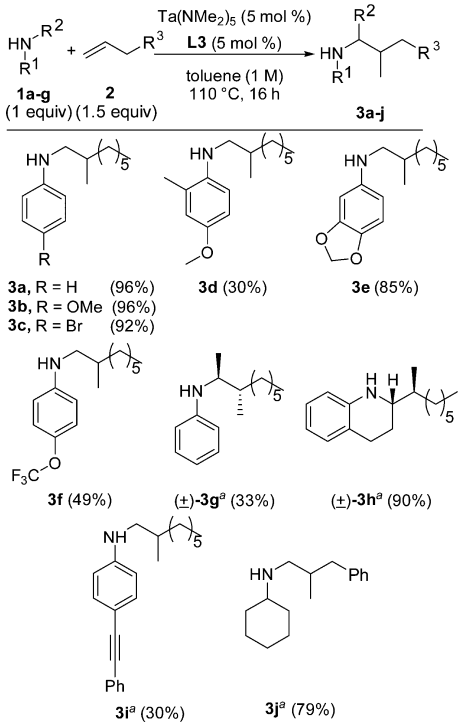
This byproduct not only increases the amount of alkene necessary to realize full conversion of the added amine substrate but also can complicate reaction purification. Given the low boiling point of dimethylamine, unwanted byproduct could be eliminated by drastically increasing the headspace within the sealed reaction vessel; either a 20 mL scintillation vial (glovebox setup) (Table 1, entry 12) or a three-neck flask with an oil bubbler outlet (syringe technique setup) (Table 1, entry 13) offer optimized product yields. The prevention of byproduct formation also leads to an increase in the relative rate of conversion, with reactions being complete within 16 h rather than 24 h (Table 1, entries 12 and 13). Prevention of byproduct formation also simplifies the workup and product purification;

DOI: 10.1021/acs.orglett.7b02149
Org. Lett. XXXX, XXX, XXX−XXX

after reaching 100% conversion, analytically pure product can be obtained without column chromatography.

With optimized conditions in hand (Table 1, entry 12), several different secondary amine substrates were tested (Scheme 3).

Scheme 3. Amine Substrate Scope



[a]10 mol % catalyst, 130 °C, 24 h.

Functionalized aniline derivatives can be tolerated (**3b**–**3f**), although the inclusion of an alkyne **3i** led to poor reactivity. *Ortho* substituents on the phenyl ring led to a significant decrease in yield (**3d**), likely due to the increased steric bulk surrounding the nitrogen. Substrates with highly polar or protic functional groups, such as ketones and hydroxyl groups, were not tolerated, but dialkylamines **3j** were reactive under more forcing conditions.

Notably, both *N*-ethylaniline **3g** and tetrahydroquinoline **3h** were useful substrates for the generation of a single diastereomer, albeit under more forcing reaction conditions. This *in situ* prepared catalyst is the first reported instance of hydroaminoalkylation with *N*-ethylaniline (Figure 4). This diastereoselectivity can be explained through the proposed mechanism of the reaction (Figure 3);[30] insertion of the alkene into

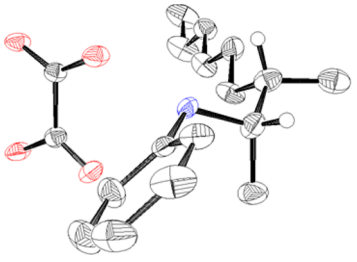
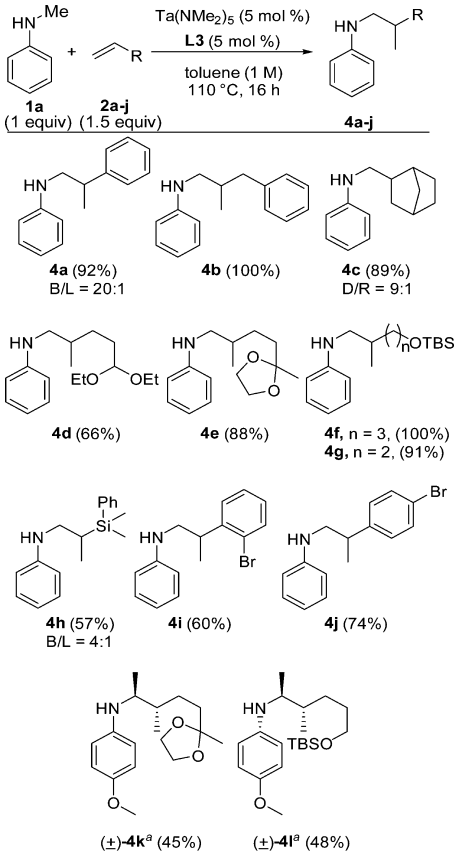


Figure 4. ORTEP representation of **3g-Oxalate** X-ray crystallographic structure. Ellipsoids plotted at 50% probability; nontertiary hydrogens omitted for clarity.

tantallaziridine **A** leads to the formation of the aza-metallacycle **B**, with the substituents in the *trans* configuration instead of the *cis* configuration (**C**) in order to minimize the steric repulsion of the substituents of the metallacycle. Thus, using this one-step catalytic reaction, α,β-alkylated amines and α,β'-heterocycles can be prepared diastereoselectively.

Various alkenes were also tested for activity (Scheme 4). Substituted styrenes **4a**, **4i**–**j** were tolerated, but with some

Scheme 4. Alkene Substrate Scope



[a]10 mol % catalyst, 130 °C, 24 h.

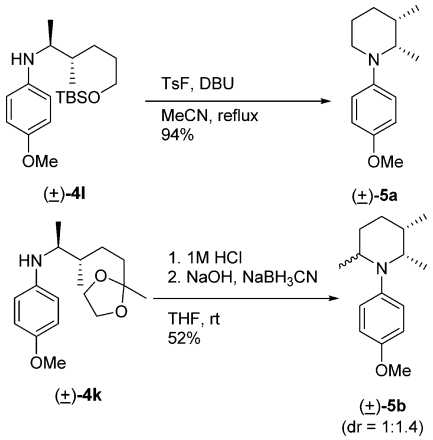
sensitivity to steric bulk in the *ortho*-position. This sensitivity to steric bulk on the alkene also results in internal alkenes and geminally disubstituted alkenes not being tolerated, regardless of reaction temperature.

Furthermore, various unactivated olefins were tolerated, including those with protected functional groups such as acetals **4d**, ketals **4e**, and TBS-protected ethers **4f**–**g**. Such functional group tolerance is notable, as it allows for functional group transformations for further synthetic elaboration, including the preparation of unsaturated *N*-heterocyclic compounds, such as piperidines (Scheme 5).[31]

Using our *in situ* prepared catalyst system, selectively alkylated PMP-protected piperidine products can be assembled in two synthetic steps. The aminoalcohol derivative **4l** can be deprotected and cyclized in a one-pot method using tosyl fluoride to produce the *cis*-dimethylated piperidine product **5a** in excellent yield.[31] As an alternative proof of concept, acidic deprotection of ketal **4k** leads to the formation of a cyclic imine, which upon reduction with sodium cyanoborohydride gives the 2,3,6-methylated product **5b**. These rapidly assembled alkylated

DOI: 10.1021/acs.orglett.7b02149
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 5. Formation of Polysubstituted Piperidines



heterocycles are precursors to free piperidine building blocks via oxidative cleavage of the 4-methoxyphenyl group.

In summary, an easy to use protocol for the *in situ* preparation of a regioselective and diastereoselective tantalum hydroaminoalkylation catalyst has been developed. This method utilizes commercially available starting materials and does not require the isolation of air- or moisture-sensitive organometallic complexes. By modifying the reaction conditions we have shown that undesirable byproduct formation, resulting from dimethylamine hydroaminoalkylation, can be avoided. This experimental procedure results in the synthesis of α- and β-alkylated amines, providing a complementary disconnection strategy for the synthesis of selectively substituted amines. We have shown that the reaction can accommodate a variety of different substrates, including *N*-ethylaniline and tetrahydroquinoline to give α,β-alkylated products diastereoselectively. This early transition metal catalyst can be used in combination with protected functionalities, thereby allowing for the synthesis of polyalkylated unsaturated *N*-heterocycles. This early stage work provides a platform for the further development of broadly applicable and user-friendly early transition metal hydroaminoalkylation catalysts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02149.

Crystallographic data for compounds **3g** and **5** (CIF)
General experimental procedures, characterization details, and ^{1}H and ^{13}C NMR spectra of compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: schafer@chem.ubc.ca.

ORCID

Laurel L. Schafer: 0000-0003-0354-2377

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Damon Gilmour (University of British Columbia) for support with X-ray crystallography. We thank National Sciences and Engineering Resource Council (NSERC) and CREATE Sustainable Synthesis for funding, and P.E. thanks the University of British Columbia for scholarship funding. This was supported in part by the Canada Research Chairs program.

■ REFERENCES

(1) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. *Chem. Soc. Rev.* **2016**, *45*, 546−576.
(2) Nauha, E.; Nissinen, M. *J. Mol. Struct.* **2011**, *1006*, 566−569.
(3) Bean, M. J.; Ramsay, J. Agrochemical composition containing activity-enhancing adjuvants. Google Patents: 2002.
(4) Lei, Y. *J. ASTM Int.* **2005**, *2*, 12172.
(5) Perry, M. R.; Ebrahimi, T.; Morgan, E.; Edwards, P. M.; Hatzikiriakos, S. G.; Schafer, L. L. *Macromolecules* **2016**, *49*, 4423−4430.
(6) Lienkamp, K.; Madkour, A. E.; Musante, A.; Nelson, C. F.; Nüsslein, K.; Tew, G. N. *J. Am. Chem. Soc.* **2008**, *130*, 9836−9843.
(7) Zheng, Z.-J.; Liu, L.-X.; Gao, G.; Dong, H.; Jiang, J.-X.; Lai, G.-Q.; Xu, L.-W. *RSC Adv.* **2012**, *2*, 2895−2901.
(8) Kobayashi, S.; Song, J.; Silvis, H. C.; Macosko, C. W.; Hillmyer, M. A. *Ind. Eng. Chem. Res.* **2011**, *50*, 3274−3279.
(9) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795−3892.
(10) Crozet, D.; Urrutigoïty, M.; Kalck, P. *ChemCatChem* **2011**, *3*, 1102−1118.
(11) Ren, T.; Patel, M.; Blok, K. *Energy* **2006**, *31*, 425−451.
(12) Meng, J.; Li, X.-H.; Han, Z.-Y. *Org. Lett.* **2017**, *19*, 1076−1079.
(13) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. *Chem. Rev.* **2015**, *115*, 2596−2697.
(14) Eisenberger, P.; Ayinla, R. O.; Lauzon, J. M. P.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 8361−8365.
(15) Herzon, S. B.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 14940−14941.
(16) Reznichenko, A. L.; Hultzsch, K. C. *J. Am. Chem. Soc.* **2012**, *134*, 3300−3311.
(17) Dörfler, J.; Preuß, T.; Schischko, A.; Schmidtmann, M.; Doye, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 7918−7922.
(18) Chong, E.; Brandt, J. W.; Schafer, L. L. *J. Am. Chem. Soc.* **2014**, *136*, 10898−10901.
(19) Zi, G.; Zhang, F.; Song, H. *Chem. Commun.* **2010**, *46*, 6296−6298.
(20) Weers, M.; Lühning, L. H.; Lührs, V.; Brahms, C.; Doye, S. *Chem. - Eur. J.* **2017**, *23*, 1237−1240.
(21) Tran, A.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2017**, *56*, 10530.
(22) Pan, S.; Endo, K.; Shibata, T. *Org. Lett.* **2011**, *13*, 4692−4695.
(23) Schinkel, M.; Wang, L.; Bielefeld, K.; Ackermann, L. *Org. Lett.* **2014**, *16*, 1876−1879.
(24) Manßen, M.; Lauterbach, N.; Dörfler, J.; Schmidtmann, M.; Saak, W.; Doye, S.; Beckhaus, R. *Angew. Chem., Int. Ed.* **2015**, *54*, 4383−4387.
(25) Zhang, Z.; Hamel, J.-D.; Schafer, L. L. *Chem. - Eur. J.* **2013**, *19*, 8751−8754.
(26) Garcia, P.; Lau, Y. Y.; Perry, M. R.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 9144−9148.
(27) Chong, E.; Garcia, P.; Schafer, L. L. *Synthesis* **2014**, *46*, 2884−2896.
(28) Brandt, J.; Chong, E.; Schafer, L. L. *ACS Catal.* **2017**, *7*, 6323.
(29) Lauzon, J. M. P.; Eisenberger, P.; Rosca, S.-C.; Schafer, L. L. *ACS Catal.* **2017**, *7*, 5921.
(30) Nugent, W. A.; Ovenall, D. W.; Holmes, S. J. *Organometallics* **1983**, *2*, 161−162.
(31) Payne, P. R.; Garcia, P.; Eisenberger, P.; Yim, J. C. H.; Schafer, L. L. *Org. Lett.* **2013**, *15*, 2182−2185.

DOI: 10.1021/acs.orglett.7b02149
Org. Lett. XXXX, XXX, XXX−XXX