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Preparative Synthesis of Highly Substituted Tetrahydropyridines via a Rh(I)-Catalyzed C−H Functionalization Sequence

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Supporting Information

ABSTRACT: We report a Rh(I)-catalyzed C−H activation/alkenylation/electrocyclization cascade and subsequent reduction for the synthesis of highly substituted tetrahydropyridines. These products can be accessed on a gram scale with low catalyst loadings and at high reaction concentrations. Additionally, a modified Rh-catalyst, prepared from $[RhCl(cod)]_2$ as a robust bench-stable precatalyst was developed to enable straightforward reaction set up without the use of a glovebox. To demonstrate the practicality of this reaction, a >100 mmol scale Rh-catalyzed cascade reaction sequence utilizing the air-stable precatalyst $[RhCl(cod)]_2$ was performed on the bench to furnish the pure tetrahydropyridine product in 93% yield.

INTRODUCTION

C−H bond functionalization has emerged as a powerful approach for the synthesis and elaboration of nitrogen heterocycles from simple precursors.[1] Previous work from our group includes the Rh(I)-catalyzed C−H activation/alkenylation/electrocyclization cascade and subsequent reduction to generate highly substituted tetrahydropyridines (Figure 1).[2,3]

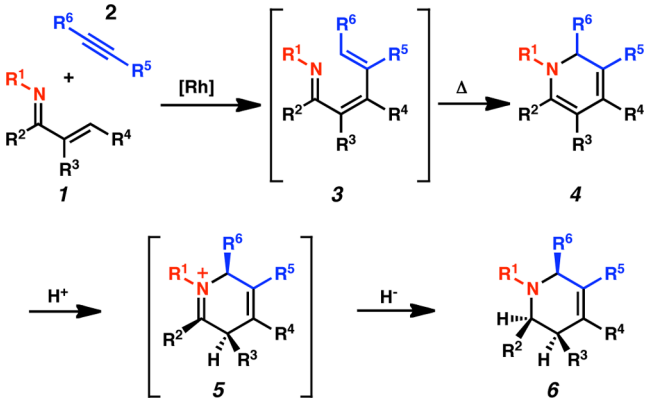

Figure 1. Rh(I)-catalyzed cascade sequence.

This transformation proceeds by Rh-catalyzed C−H bond activation of α,β-unsaturated imine **1** followed by addition across alkyne **2** to generate azatriene **3**, which undergoes in situ 6π-electrocyclization to afford 1,2-dihydropyridine **4**.[4] Subsequent stereoselective protonation of the enamine double bond and reduction of the resulting iminium **5** delivers tetrahydropyridine **6**.

In the initial reports from our group, the Rh(I)-catalyzed cascade reaction of imines and alkynes was surveyed over a wide range of substrates to deliver various tetrahydropyridines in excellent yield and diastereoselectivity. A variety of nitrogen substituents were successfully employed, including benzyl, aryl, and different alkyl groups. The sequence also proceeded in good overall yields for imines with a variety of substitution patterns at the R^2 to R^4 positions, including examples where one or more of the sites were left unsubstituted and with alkyl, aromatic, or heteroaromatic functionality introduced. For fully substituted imines, tetrahydropyridine products were consistently produced with >95% diastereoisomeric purity, including fused bicyclic products obtained from cyclic imine precursors.

Although 3-hexyne (**13**) was utilized as the alkyne substrate for the majority of these reactions, various other internal alkynes proved to be competent coupling partners. Terminal alkynes are not suitable inputs due to competitive homocoupling under the reaction conditions. For this reason, silyl alkynes were developed as terminal alkyne surrogates to provide tetrahydropyridines with high stereo- and regiocontrol (Figure 2). Concomitant cleavage of the silyl moiety occurs

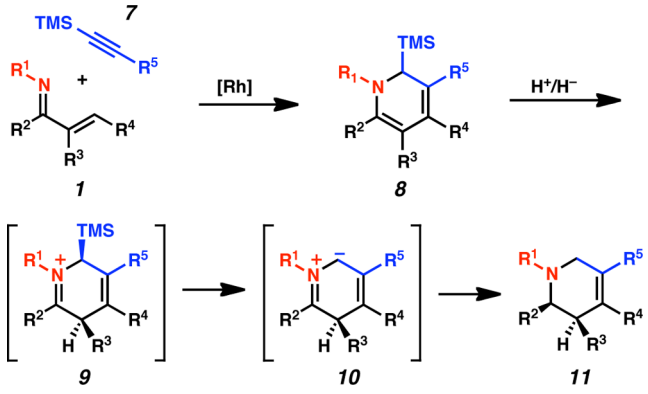

Figure 2. Rh-catalyzed cascade with silyl alkynes.

during the stereoselective protonation/reduction of the silyl dihydropyridine intermediate **8**. For this sequence, TMS-alkynes substituted with electron-rich and electron-poor aromatics and alkyl chains displaying a variety of functionality proved to be effective substrates.

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RESULTS AND DISCUSSION

In the previously disclosed results, the sequence was typically run on 0.25−0.5 mmol scale and with 1−2.5 mol % of $[RhCl(coe)_2]_2$ (coe = cyclooctene) as the precatalyst, which is air- and moisture-sensitive and therefore was stored and manipulated in a glovebox. In this article, we report the Rh(I)-cyclization cascade reaction for the synthesis of tetrahydropyridines on significantly larger scale, at high concentrations, and with low catalyst loadings. Moreover, conditions have been developed that enable the reaction to be performed on the benchtop with $[RhCl(cod)]_2$ as a robust, air-stable precatalyst.

To improve the utility and practicality of this reaction, we sought to decrease the catalyst loading while concurrently increasing reaction concentration to minimize waste and reduce reactor size. For our optimization studies, we used imine **12** and 3-hexyne (**13**) to affect the desired transformation using low catalyst loadings of $[RhCl(coe)_2]_2$. Different catalyst loadings, reaction times, and concentrations were evaluated. Utilizing optimized conditions, the rhodium-catalyzed C−H activation/alkenylation/electrocyclization was performed with α,β-unsaturated imine **12** at 1.5 M in toluene with only 1.5 equiv of alkyne **13**. Moreover, only 0.25 mol % of $[RhCl(coe)_2]_2$, and 0.5 mol % of the commercially available ligand, 4-(diethylphosphino)-*N*,*N*-dimethylaniline[5] provided complete conversion to the dihydropyridine intermediate at 80 °C after 24 h. The dihydropyridine solution was then directly transferred to a heterogeneous solution of $NaBH(OAc)_3$ in ethanol at 0 °C, and excess acetic acid was subsequently added. Tetrahydropyridine **14** was isolated in 87% yield from 1 g of imine **12** (Figure 3). Additionally, tetrahydropyridine with an

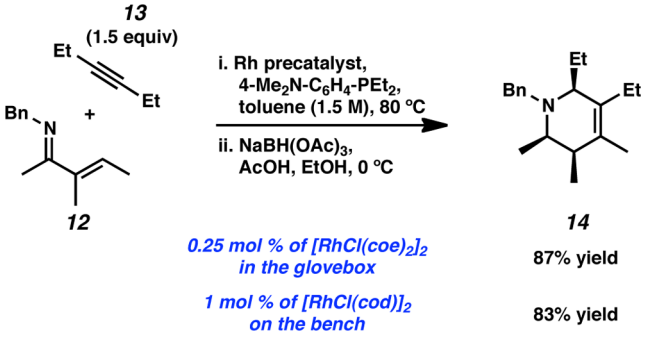

Figure 3. Synthesis of tetrahydropyridine **14** via a Rh-catalyzed cascade.

appended furyl group **16** was obtained in analytically pure form in 80% yield also from 1 g of imine **15** (Figure 4). Under these optimal conditions, complete coupling was again observed with only 1.5 equiv of the alkyne coupling partner **13**.

While the aforementioned gram scale reactions with 0.25 mol % of the $[RhCl(coe)_2]_2$ precatalyst resulted in complete conversion and excellent overall yields of tetrahydropyridines **14** and **16**, a glovebox was used to manipulate and store $[RhCl(coe)_2]_2$ due to its air and moisture sensitivity. We therefore chose to identify a robust, air-stable precatalyst that would enable the transformation to be performed on the benchtop without any use of a glovebox. This was accomplished by employing $[RhCl(cod)]_2$, which is well-documented to be completely stable in air at room temperature due to the strong metal coordination of the bidentate cyclooctadiene ligand.[6] When $[RhCl(cod)]_2$ was used as the

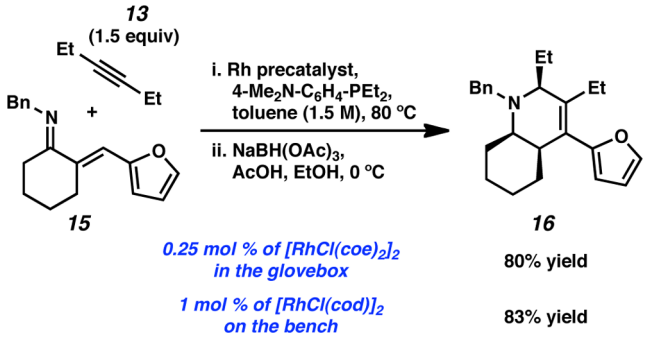

Figure 4. Synthesis of tetrahydropyridine **16** via a Rh-catalyzed cascade.

precatalyst, we found that a 1 h initiation period with the phosphine ligand 4-(diethylphosphino)-*N*,*N*-dimethylaniline in toluene was necessary to dissociate the bidentate ligand and to generate the active catalyst.[7] A higher but certainly acceptable catalyst loading of 1 mol % of $[RhCl(cod)]_2$ was also necessary to achieve complete conversion within a 24 h period. Importantly, the reaction can be performed on the benchtop using standard inert atmosphere techniques. Tetrahydropyridines **14** and **16** were generated from 1 g of imines **12** and **15** in similar yields using the air-stable precatalyst, $[RhCl(cod)]_2$ (Figures 3 and 4, respectively). Experiments utilizing 0.5 mol % of $[RhCl(cod)]_2$ as the precatalyst at 100 °C were also examined. However, at this higher temperature the tetrahydropyridine **14** was obtained in 70% yield, which is significantly lower than observed for the analogous transformation performed at 80 °C. Based upon NMR monitoring of the reaction, we believe that the dihydropyridine intermediate is susceptible to side reactions at this higher temperature.

We next applied the optimal conditions for the Rh-reaction with silyl alkynes as a coupling partner. Upon subjection of imine **12** and only 1.2 equiv of indole silyl alkyne **17** to 0.25 mol % of $[RhCl(coe)_2]_2$ as the precatalyst with 0.50 mol % of 4-(diethylphosphino)-*N*,*N*-dimethylaniline, a significant amount of starting material imine **12** was present after 24 h at 80 °C. Increasing the catalyst loading to 0.5 mol % of $[RhCl(coe)_2]_2$ led to complete conversion to the silyl dihydropyridine intermediate. With an effective catalyst loading identified for this system, imine **12** and indole silyl alkyne **17** were subjected to the Rh(I)-cascade sequence on 1 g of imine **12** to provide the desired tetrahydropyridine **18** in 86% yield (Figure 5). Additionally, we performed a benchtop reaction with silyl alkyne **17** using the air-stable precatalyst $[RhCl(cod)]_2$. An increase in catalyst loading to 1.5 mol % of $[RhCl(cod)]_2$ was required to achieve complete conversion in

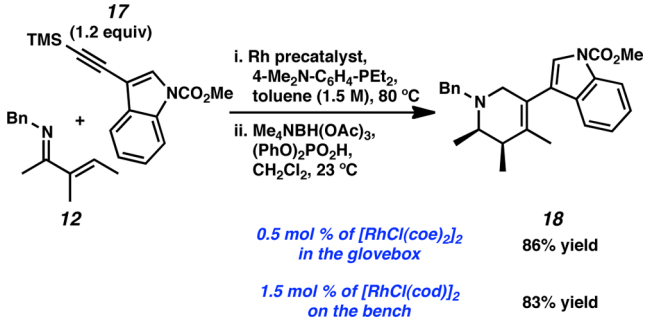

Figure 5. Synthesis of tetrahydropyridine **18** via silyl alkynes.

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the Rh-catalyzed C−H activation/alkenylation/electrocyclization sequence. After subsequent reduction, the tetrahydropyridine **18** was obtained in 83% yield (Figure 5). A Rh-cyclization cascade utilizing 1 mol % of $[RhCl(cod)]_2$ at 100 °C with imine **12** and indole silyl alkyne **17** led to a slight decrease in yield to 77%.

To further test the scalability of this method, a reaction with 20 g (>100 mmol) of imine **12** was treated with alkyne **13** to generate tetrahydropyridine **14** (Figure 6). Preparation of imine

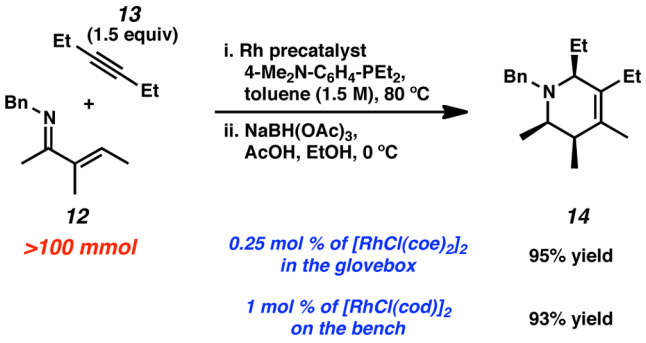

Figure 6. Rh(I)-catalyzed cyclization cascade on >100 mmol scale.

12 is achieved by the $Ti(OEt)_4$-mediated coupling of the corresponding enone and benzylamine.[8] For the previously reported 1 g reaction scale, the imine **12** was taken on to the Rh-catalyzed cyclization after simple extraction and without any purification. However, given the low catalyst loading of 0.25 mol % of the $[RhCl(coe)_2]_2$ precatalyst, the possibility for catalyst inactivation with only a small amount of impurities was a concern. Thus, for the larger scale reaction the imine was first purified by distillation. With this purified imine, the Rh-catalyzed cascade reaction on 20 g (>100 mmol) of imine **12** gave complete conversion to the dihydropyridine intermediate in high purity within 24 h as established by ^1H NMR analysis.

Initial attempts at the reduction of the dihydropyridine intermediate on this larger scale led to incomplete conversion to the desired tetrahydropyridine. In the experimental protocol, $NaBH(OAc)_3$ and ethanol are cooled to 0 °C followed by the addition of the dihydropyridine solution. Acetic acid is added to the flask and the reaction is stirred at 0 °C for 3 h. On smaller scales, including the 1 g scale discussed previously, the $NaBH(OAc)_3$ and ethanol had been premixed within 10 min of addition of the dihydropyridine. However, in our initial attempts on the larger scale, the $NaBH(OAc)_3$ and ethanol were premixed for much longer times (>35 min), which resulted in inactivation of the reductant. To obtain the product of kinetic protonation (Figure 1), it is essential that the iminium only be generated in the presence of the reductant to prevent equilibration to the thermodynamically more stable conjugated iminium isomer.[3d] This requires that the dihydropyridine be added to excess $NaBH(OAc)_3$ in ethanol followed by addition of acetic acid. The reaction setup was therefore modified to maintain the described order of reagent additions while minimizing the $NaBH(OAc)_3$ and ethanol mixing time. Importantly, the internal temperature was measured throughout the course of the reaction, which established that significant exotherms did not occur during any of the reagent addition steps.

In the optimized reaction setup, $NaBH(OAc)_3$ was added in one portion to precooled ethanol at 0 °C with no exotherm observed upon addition. The room temperature Rh-cascade reaction solution containing the dihydropyridine was then immediately added to the $NaBH(OAc)_3$ in ethanol over 2 min. During the addition, the temperature of the reaction solution increased from 0 to 2 °C. By GC analysis, a majority of tetrahydropyridine **14** had already formed before the addition of acetic acid, presumably due to the presence of acetic acid in $NaBH(OAc)_3$. A large excess of acetic acid (26 equiv) was then added to the flask over 5 min and resulted in a final temperature of 7 °C by the end of the addition. In our earlier report,[3e] a large excess of the inexpensive acetic acid was used, but it is likely that at least for this dihydropyridine, the number of equivalents of acetic acid can be dramatically reduced.[3e] The reduction proceeded to complete conversion within 2 min as determined by GC analysis, and the reaction solution was allowed to warm to 23 °C after 1 h. After concentration and then dilution with ethyl acetate and water, the aqueous phase was taken to a pH of 11 by addition of 2 M sodium hydroxide. The organic phase was isolated after extraction with ethyl acetate, washed with brine, dried over sodium sulfate, and concentrated to give the desired tetrahydropyridine **14** in quantitative yield in pure form with >99% purity by GC and NMR analysis (see the Supporting Information). However, the unpurified oil was brown in color due to trace rhodium impurities, and it therefore was filtered through a plug of silica (10 cm × 6 cm, 450 mL) with 400:25:3 hexanes−EtOAc−Et_3N as eluent to yield tetrahydropyridine **14** in 95% yield as a pale yellow oil.

Additionally, a 20 g (>100 mmol) reaction of imine **12** with alkyne **13** was conducted utilizing the robust, air-stable precatalyst $[RhCl(cod)]_2$ (Figure 6). The Rh-catalyzed activation/alkenylation/electrocyclization, which was set up on the bench utilizing standard inert atmosphere techniques, underwent complete conversion to the dihydropyridine. Subsequent reduction afforded tetrahydropyridine **14** in 93% yield after silica gel filtration.

■ CONCLUSION

In conclusion, we have reported the synthesis of highly substituted tetrahydropyridines on gram scale with low catalyst loadings in excellent yield. To eliminate the use of a glovebox, we have developed a protocol that can be performed on the benchtop using the robust, air-stable precatalyst $[RhCl(cod)]_2$. Additionally, this reaction sequence was performed on a larger scale (>100 mmol) to deliver the desired tetrahydropyridine product in 93−95% yield. We are hopeful that the reported procedure for the synthesis of tetrahydropyridines on preparative scales at low catalyst loadings under convenient conditions will be useful to the pharmaceutical industry.

■ EXPERIMENTAL SECTION

General Procedure for the Rh-Catalyzed Cascade Reaction Using $[RhCl(coe)_2]_2$. A 20 mL vial was charged with $[RhCl(coe)_2]_2$ (0.25 mol %), 4-(diethylphosphino)-*N*,*N*-dimethylaniline (0.5 mol %), and toluene, all in a glovebox. This mixture was transferred to an oven-dried 50 mL three-neck flask equipped with a stir bar and a reflux condenser. The alkyne (1.5 equiv) was added to the flask followed by the imine (1.0 g, 1.0 equiv, 1.5 M final concentration). The flask was removed from the glovebox, and the reaction mixture was stirred at 80 °C under nitrogen. After 24 h, the reaction mixture was allowed to cool to 23 °C before being taken on to the reduction step.

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General Procedure for the Rh-Catalyzed Cascade Reaction Using [RhCl(cod)]$_2$. An oven-dried three-neck 50 mL flask equipped with a stir bar and reflux condenser was charged with [RhCl(cod)]$_2$ (1.0 mol %) and 4-(diethylphosphino)-*N*,N-dimethylaniline (2.0 mol %). The flask was purged with nitrogen for 5 min. Toluene was added, and the resulting mixture was stirred at 23 °C under nitrogen for 1 h. The alkyne (1.5 equiv) was added to the flask followed by the imine (1.0 g, 1.0 equiv, 1.5 M final concentration). The reaction mixture was stirred at 80 °C under nitrogen for 24 h and then was allowed to cool to 23 °C before being taken on to the reduction step.

General Dihydropyridine Reduction Procedure for an Internal Alkyne Coupling Partner. To a separate oven-dried 250 mL round-bottom flask equipped with a stir bar were added NaBH(OAc)$_3$ (3.0 equiv) and ethanol. The flask was placed in a 0 °C ice bath, and within 10 min, the crude dihydropyridine solution (from the Rh reaction) was added via cannula or syringe transfer. Acetic acid was added to the flask, and the reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was allowed to warm to 23 °C and then was evaporated to dryness. EtOAc (20 mL) and H_2O (10 mL) were added to the flask. 2 M NaOH was added to the mixture until the pH of the aqueous layer was >11. The mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography to afford the desired tetrahydropyridine.

General Dihydropyridine Reduction Procedure for a Silyl Alkyne as a Coupling Partner. To a separate oven-dried 250 mL round-bottom flask was added tetramethylammonium triacetoxyborohydride (3.0 equiv). The flask was submersed in a 23 °C water bath, and CH_2Cl_2 was added under nitrogen. The resulting mixture was stirred until homogeneous. The crude dihydropyridine solution (from the Rh reaction) was added to the flask via cannula or syringe transfer with the aid of CH_2Cl_2, and the solution was vigorously stirred (>1000 rpm). Diphenyl phosphate (2.2 equiv) in CH_2Cl_2 was added over 10 min. The homogeneous mixture was stirred at 23 °C under nitrogen for 12 h. The reaction was quenched with 1 M NaOH (100 mL), and the mixture was stirred vigorously until gas evolution ceased (approximately 20 min). The mixture was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (150 mL) followed by a final extraction of the aqueous phase with CH_2Cl_2 (50 mL). The organic layers were dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by flash chromatography to deliver the product tetrahydropyridine.

*Procedure for the Rh-Cascade Reaction Using [RhCl(coe)$_2$]$_2$ Precatalyst, and Reduction Sequence at >100 mmol Scale for the Synthesis of 1-Benzyl-5,6-diethyl-2,3,4-trimethyl-1,2,3,6-tetrahydropyridine (**14**).* A 20 mL vial was charged with [RhCl(coe)$_2$]$_2$ (192 mg, 0.267 mmol, 0.25 mol %), 4-(diethylphosphino)-*N*,*N*-dimethylaniline (112 mg, 0.534 mmol, 0.5 mol %), and toluene (12 mL), all in a glovebox. This mixture was transferred to an oven-dried 250 mL three-neck flask equipped with a stir bar and a reflux condenser. Toluene (60 mL) was added to the flask. 3-Hexyne (**13**) (18.2 mL, 160 mmol, 1.5 equiv) was added to the flask followed by the imine **12** (20.0 g, 107 mmol, 1 equiv). The flask was removed from the glovebox, and the reaction mixture was stirred at 80 °C under nitrogen. After 24 h, the reaction mixture was allowed to cool to 23 °C. A 2 L three-neck Morton flask was assembled with a thermometer, an addition funnel, and a Claisen adapter (one neck attached to a nitrogen line and the other neck attached to an external bubbler). Ethanol (594 mL) was added to the flask, which was cooled to 0 °C in an ice bath. The crude dihydropyridine was transferred to the addition funnel via cannula. The flask was rinsed with toluene (10 mL), and that solution was also transferred to the addition funnel via cannula. Sodium triacetoxyborohydride (68.0 g, 320 mmol, 3 equiv) was added via a funnel in one portion (by temporarily removing the thermometer) to the precooled ethanol with stirring (>750 rpm). The crude dihydropyridine was then immediately added to the heterogeneous mixture via an addition funnel over a period of 2 min, and at the end of the addition, the internal temperature of the mixture had warmed to 2 °C. The addition funnel was rinsed with toluene (10 mL), and the rinse was also added to the reaction solution. Acetic acid (160 mL, 2.78 mol, 26 equiv) was added to the flask under nitrogen with stirring in an ice bath over 4 min at which time the internal temperature had increased to 7 °C. After stirring for 1 h in an ice bath, the reaction mixture was allowed to warm to 23 °C, and the volatiles were evaporated. EtOAc (50 mL) and H_2O (25 mL) were added to the flask. 2 M NaOH was added to the mixture until the pH of the aqueous layer was >11. The mixture was extracted with EtOAc (4 × 150 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was filtered over a plug of 450 mL of silica (400:25:3 hexanes−EtOAc−Et_3N eluent) and concentrated under reduced pressure to yield tetrahydropyridine **14** as a yellow oil (27.5 g, 95% yield). Spectral data describing the product purity after crude work up and after silica gel filtration can be found in the Supporting Information.

*Procedure for the Rh-Cascade Reaction Using [RhCl(cod)]$_2$ Precatalyst and Reduction Sequence at >100 mmol Scale for the Synthesis of 1-Benzyl-5,6-diethyl-2,3,4-trimethyl-1,2,3,6-tetrahydropyridine (**14**).* An oven-dried three-neck 250 mL flask equipped with a stir bar and reflux condenser was charged with [RhCl(cod)]$_2$ (527 mg, 1.07 mmol, 1 mol %) and 4-(diethylphosphino)-*N*,*N*-dimethylaniline (447 mg, 2.14 mmol, 2 mol %). The flask was purged with nitrogen for 5 min. Toluene (72 mL) was added, and the resulting mixture was stirred at 23 °C under nitrogen for 1 h. 3-Hexyne (**13**) (18.2 mL, 160 mmol, 1.5 equiv) was added to the flask followed by the imine **12** (20.0 g, 107 mmol, 1 equiv). The reaction mixture was stirred at 80 °C under nitrogen. After 24 h, the reaction mixture was allowed to cool to 23 °C. A 2 L three-neck Morton flask was assembled with a thermometer, an addition funnel, and a Claisen adapter (one neck attached to a nitrogen line and the other neck attached to an external bubbler). Ethanol (594 mL) was added to the flask and cooled to 0 °C in an ice bath. The dihydropyridine solution was transferred to the addition funnel via cannula. The flask was rinsed with toluene (10 mL), and that solution was transferred to the addition funnel via cannula. Sodium triacetoxyborohydride (68.0 g, 320 mmol, 3 equiv) was added via funnel in one portion (by temporarily removing the thermometer) to the precooled ethanol with stirring (>750 rpm). The dihydropyridine solution was then immediately added to the heterogeneous mixture via addition funnel over a period of 2 min, and at the end of the addition, the internal temperature of the mixture had warmed to 2 °C. The addition funnel was rinsed with toluene (10 mL), and the

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rinse was also added to the reaction solution. Acetic acid (160 mL, 2.78 mol, 26 equiv) was added to the flask under nitrogen with stirring over 4 min at which time the internal temperature had increased to 7 °C. After stirring for 1 h in an ice bath, the reaction mixture was allowed to warm to 23 °C, and the volatiles were evaporated. EtOAc (50 mL) and H_2O (25 mL) were added to the flask. 2 M NaOH was added to the mixture until the pH of the aqueous layer was >11. The mixture was extracted with EtOAc (4 × 150 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was filtered over a silica plug (10 cm × 6 cm, 450 mL of silica with 400:25:3 hexanes−EtOAc−Et_3N eluent) and concentrated under reduced pressure to yield tetrahydropyridine **14** as a pale yellow oil (26.85 g, 93% yield). Spectral data describing the product purity after crude work up and after silica gel filtration can be found in the Supporting Information.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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(5) 4-(Diethylphosphino)-*N*,*N*-dimethylaniline is commercially available from Sigma-Aldrich (CAS No. 17005-57-1) at an approximate cost of $90 US/gram and can be prepared via the procedure described in ref 3c.

(6) For recent examples of C−H activation using $[RhCl(cod)]_2$, see: (a) Kuninobu, Y.; Nakahara, T.; Takeshima, H.; Takai, K. *Org. Lett.* **2013**, *15*, 426. (b) Zhao, X.; Yu, Z. *J. Am. Chem. Soc.* **2008**, *130*, 8136. (c) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2005**, *7*, 2229.

(7) Storgaard, M.; Ellman, J. A. *Org. Synth.* **2009**, *86*, 360.

(8) (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 5604. For the titanium-mediated preparation of imines using EDTE, see: (b) Reeves, J. T.; Tan, Z.; Han, Z. S.; Li, G.; Zhang, Y.; Xu, Y.; Reeves, D. C.; Gonnella, N. C.; Ma, S.; Lee, H.; Lu, B. Z.; Senanayake, C. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 1400.