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

Tehetena Mesganaw and Jonathan A. Ellman*

Department of Chemistry, Yale University, New Haven, Connecticut 06520, United States

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. 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). 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. 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 R² to R⁴ 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 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.

Received: July 8, 2014
Published: August 29, 2014
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(cod)]_2 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. 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 and 0.5 mol % of the commercially available ligand, 4-(diethylphosphino)-N,N-dimethylaniline 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 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 [RhCl(coe)]_2 precatalyst resulted in complete conversion and excellent overall yields of tetrahydropyridines 14 and 16, a glovebox was used to manipulate and store [RhCl(cod)]_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. When [RhCl(cod)]_2 was used as the 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. 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 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 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(1)-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 3. Synthesis of tetrahydropyridine 14 via a Rh-catalyzed cascade.

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

Figure 5. Synthesis of tetrahydropyridine 18 via silyl alkynes.
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 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, 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 were cooled to 0 °C followed by 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–Et3N 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.** A 20 mL vial was charged with [RhCl(coe)]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.
**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 H₂O (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 Na₂SO₄, 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 tetramethylmonium triacetoxyborohydride (3.0 equiv). The flask was submersed in a 23 °C water bath, and CH₂Cl₂ 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 CH₂Cl₂, and the solution was vigorously stirred (>1000 rpm). Diphosphorus (2.2 equiv) in CH₂Cl₂ 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 CH₂Cl₂ (2 × 50 mL). The combined organic layers were washed with brine (150 mL) followed by a final extraction of the aqueous phase with CH₂Cl₂ (50 mL). The organic layers were dried over MgSO₄ 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(cod)]₂ Precatalyst and Reduction Sequence at >100 mmol Scale for the Synthesis of 1-Benzyl-5,6-diethyl-2,3,4-trimethyldihydropyridine (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 (18.1 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 H₂O (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 Na₂SO₄, and concentrated under reduced pressure. The crude product was filtered over a plug of 450 mL of silica (400:25:3 hexanes–EtOAc–Et₃N 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 (18.1 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...
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 H2O (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 Na2SO4, 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–Et3N 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

1 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

Corresponding Author

*E-mail: jonathan.ellman@yale.edu.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the NIH under grant no. GM069559 (J.A.E.) and GM069559-11S1 for postdoctoral fellowship support (T.M.).

REFERENCES

(1) For recent reviews on heterocycle synthesis via C–H activation, see: (a) Ackerman, L. Acc. Chem. Res. 2014, 47, 281. (b) Zhang, X.-S.; Chen, K.; Shi, Z.-J. Chem. Soc. Chem. 2014, 5, 2146. (c) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. Acc. Chem. Res. 2012, 45, 788. (d) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. Angew. Chem., Int. Ed. 2012, 51, 8960. (e) Song, G.; Wang, F.; Li, X. Chem. Soc. Rev. 2012, 41, 3651. (f) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. Acc. Chem. Res. 2012, 45, 814. (g) Mei, T.-S.; Kou, L.; Ma, S.; Engle, K. M.; Yu, J.-Q. Synthesis 2012, 1778. (h) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. Chem. Soc. Rev. 2011, 40, 4740. (i) McMurray, L.; O’Hara, F.; Gaunt, M. J. Chem. Soc. Rev. 2011, 40, 1885. (j) Colby, D. A.; Bergman, R. G.; Ellman, J. A. Chem. Rev. 2010, 110, 624. (k) Satoh, T.; Miura, M. Chem.—Eur. J. 2010, 16, 11212. (l) Rubin, M.; Sromek, A. W.; Gervygang, V. Synlett 2003, 15, 2265.

(2) For an accompanying review in this issue that summarizes our Rh-catalyzed synthesis approaches for the preparation of tetrahydropyridines, see: Mesganaw, T.; Ellman, J. A. Org. Process Res. Dev. 2014, 18, 1105–1109.

(3) (a) Duttwyler, S.; Chen, S.; Lu, C.; Mercado, B. Q.; Bergman, R. G.; Ellman, J. A. Angew. Chem., Int. Ed. 2014, 53, 3877. (b) Ischay, M. A.; Takase, M. K.; Bergman, R. G.; Ellman, J. A. J. Am. Chem. Soc. 2013, 135, 2478. (c) Martin, R. M.; Bergman, R. G.; Ellman, J. A. Org. Lett. 2013, 15, 444. (d) Duttwyler, S.; Chen, S.; Takase, M. K.; Wisberg, K. B.; Bergman, R. G.; Ellman, J. A. Science 2013, 339, 678. (e) Duttwyler, S.; Lu, C.; Rheiingold, A. L.; Bergman, R. G.; Ellman, J. A. J. Am. Chem. Soc. 2012, 134, 4064.

(4) For recent reviews on the synthesis and elaboration of 1,2-dihydropyridines, see: (a) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. Chem. Rev. 2012, 112, 2642. (b) Silva, E. M. P.; Varandas, P. A. M. M.; Silva, A. M. S. Synthesis 2013, 45, 3053. (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)], 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.; Mura, 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.