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Review

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Convergent Synthesis of Diverse Tetrahydropyridines via Rh(I)-Catalyzed C−H Functionalization Sequences

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ABSTRACT: A Rh-catalyzed C−H bond activation/alkenylation/electrocyclization cascade reaction provides diverse 1,2-dihydropyridines from simple and readily available precursors. The reaction can be carried out at low (<1%) Rh-catalyst loadings, and the use of the robust, air-stable Rh precatalyst, $[RhCl(cod)]_2$, enables the cascade reaction to be easily performed on the benchtop. The 1,2-dihydropyridine products serve as extremely versatile synthetic intermediates for further elaboration often without isolation. The addition of electrophiles under kinetic or thermodynamic conditions provides a wide range of iminiums. Subsequent addition of a nucleophile then generates a diverse array of differently substituted piperidine products. Additionally, [3 + 2] and [4 + 2] cycloadditions of the 1,2-dihydropyridine intermediate provides access to bridged bicyclic structures such as tropanes and isoquinuclidines. These concise reaction sequences enable the formation of highly substituted piperidines in synthetically useful yields with excellent diastereoselectivity.

INTRODUCTION

The piperidine motif is present in numerous therapeutic agents that have had exceptional biomedical impact and blockbuster status (Figure 1).[1−3] A noteworthy feature of these drugs is the truly diverse display of functionality about the piperidine core, which includes fused and bridged multicyclic rings, multiple stereogenic centers, and even quaternary carbons. Motivated by the importance of the piperidine motif, we have developed a convergent approach to access a very large array of piperidines from simple and readily available precursors.[4] This approach is centered upon a Rh-catalyzed C−H activation/alkenylation/electrocyclization cascade to provide 1,2-dihydropyridines[5,6] (Figure 2). These intermediates are amenable to further elaboration into a wide area of piperidine structures, including fused and bridged bicyclic systems as well as derivatives with low to very high levels of substitution. Importantly, the sequence requires only a couple of synthetic operations and proceeds in high overall yields and with excellent regio- and diastereocontrol, often with only a single purification step. In this review, we survey the diversity of structures that can be accessed by this approach.[4]

Several years ago we began an investigation of Rh(I)-catalyzed β-C−H bond functionalization of α,β-unsaturated imines **1** because we recognized that a very large variety of these inputs could easily be prepared from the large number of readily available α,β-unsaturated aldehydes and ketones and the vast array of commercially available primary amines (Figure 2).[7] Using $[RhCl(coe)_2]_2$ (coe = cyclooctene) as the precatalyst and the now commercially available 4-(diethylphosphino)-*N*,*N*-dimethylaniline as ligand, β-alkenylation of α,β-unsaturated imines **1** with alkynes **2** cleanly provided azatrienes **3**, which undergo in situ 6π-electrocyclization to give 1,2-dihydropyridines **4** (Figure 2).[7] This new approach provides a powerful entry to this compound class because a range of substitution patterns can be introduced using simple and readily available precursors. We first capitalized on the versatility of the 1,2-dihydropyridines **4** by their conversion to pyridines, which are present in numerous drugs.[8,9]

However, our primary aspiration was to elaborate the 1,2-dihydropyridine **4** to piperidines, which is a much more challenging goal because both regio- and diastereoselective functionalization of **4** would be required. We envisioned that reaction of dihydropyridine **4** with an electrophile under kinetic control would proceed at the α-position to give iminium **5** (Figure 3).[4d] Subsequent addition of a nucleophile would then provide tetrahydropyridine **6**. Alternatively, the reaction of dihydropyridine **4** with an electrophile under thermodynamic control should proceed at the γ-position to give a conjugated iminium **7** (Figure 3).[4d] Nucleophilic attack would then provide tetrahydropyridine **8**. Additional transformations of 1,2-dihyropyridine **4** to provide bridged bicyclic products are also possible (vide infra).[4b,c]

PIPERIDINES SYNTHESIZED FROM KINETIC IMINIUM INTERMEDIATES

Our initial demonstration of this approach proceeded by the stereoselective protonation and in situ reduction of the resulting kinetically formed iminium **5**.[4e] Although the reduction of dihydropyridines to tetrahydropyridines via iminium intermediates has been previously reported, examples where stereogenic centers were introduced were uncommon. A solution of $NaBH(OAc)_3$ and acetic acid in ethanol provide mild and convenient conditions for performing the desired protonation and reduction sequence to prepare highly substituted tetrahydropyridines.[10,11] This enabled the formation of three new stereogenic centers with excellent diastereoselectivity for both the protonation and the reduction steps (Table 1).

Kinetic protonation occurs with high diastereoselectivity because the R^6 substituent blocks one face of the dihydropyridine as a result of its pseudoaxial display enforced by A-1,2-strain.[4e] Reduction then proceeds from the face opposite both

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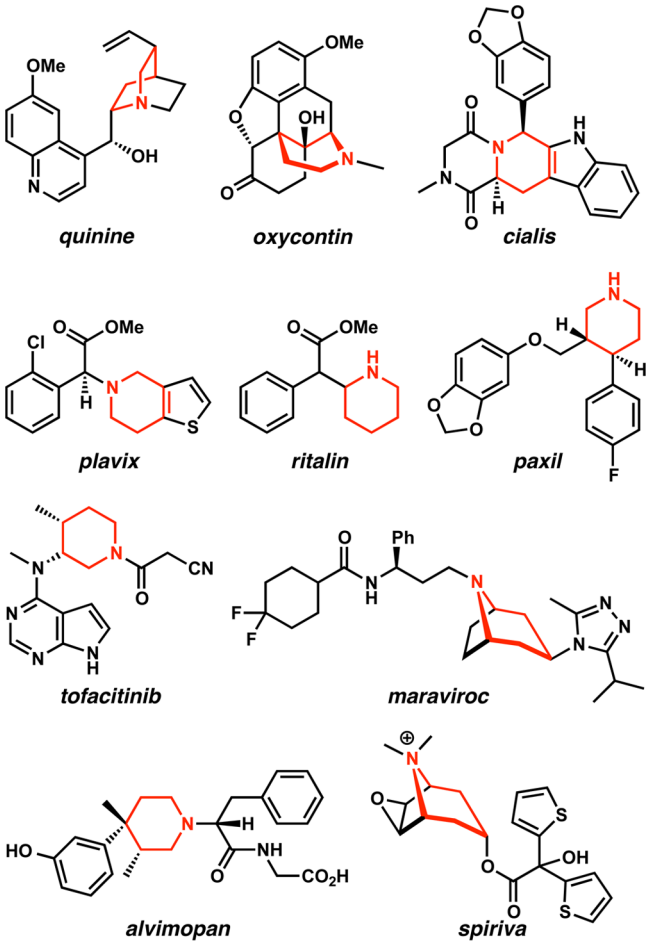


Figure 1. Representative drugs that incorporate the piperidine motif.

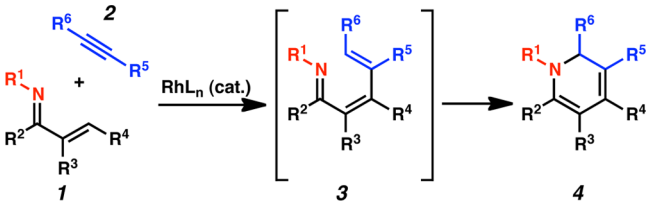


Figure 2. Rh-catalyzed activation/alkenylation/electrocyclization.

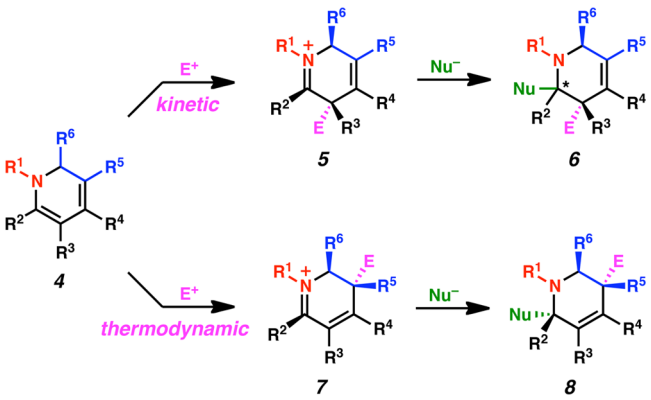
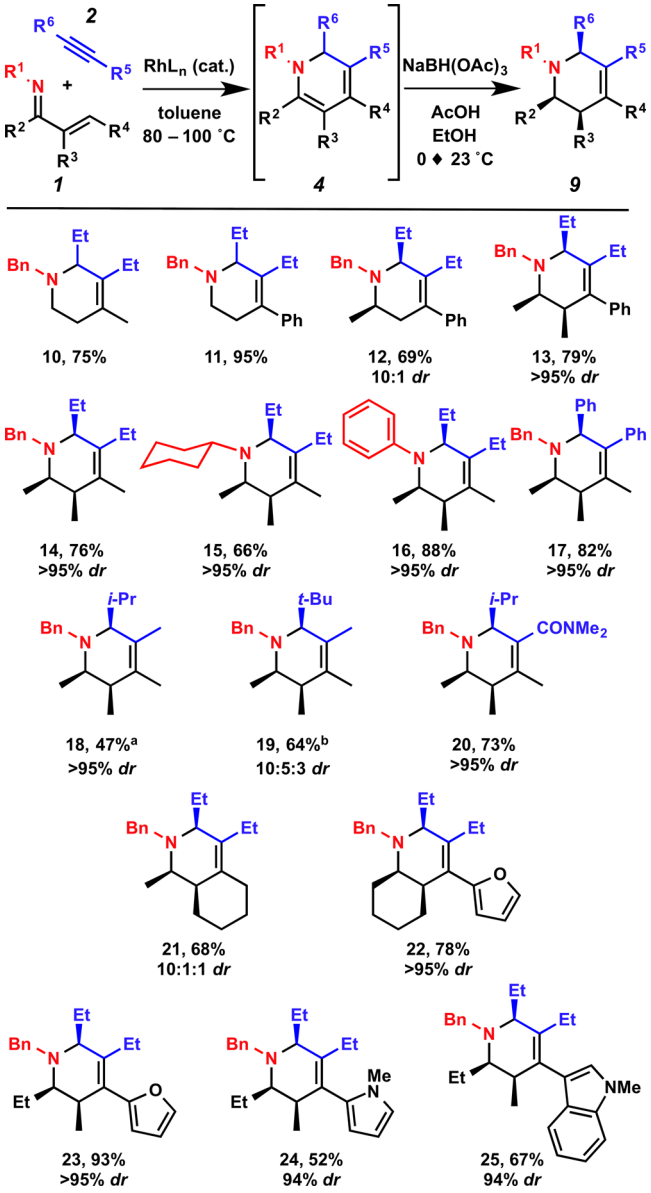


Figure 3. Piperidines generated via kinetic and thermodynamic iminiums.

the R^6 and the R^2 substituents. From a practical perspective, it is noteworthy that the reaction solution containing the 1,2-dihydropyridine intermediate is directly submitted to the protonation/reduction conditions and that the overall yields of the tetrahydropyridines as based upon the starting material imines are generally high.

The method is tolerant of various substitution patterns, including both alkyl and aryl substitution or without substitution at positions R^2–R^4 of imine **1** (Table 1).[4e] Moreover, different types of fused bicyclic piperidines, **21** and **22**, can be accessed by incorporating endo- and exocyclic imines, respectively. Imines with sterically and electronically diverse *N*-substituents such as benzyl, phenyl, and branched alkyl underwent smooth coupling with alkynes and subsequent protonation/reduction to yield tetrahydropyridines **10**–**25** in good yields and with high diastereoselectivities. Although 3-hexyne was utilized in the majority of these transformations, diphenylacetylene proved to be a competent coupling partner to yield **17** in 82% yield. Unsymmetrical alkynes were also

Table 1. Rh-catalyzed cyclization with kinetic protonation and reduction



[a]Alkyne regioselectivity 2:1; combined yield for separate regioisomers. [b]Combined yield for regioisomerically pure diastereomeric mixture.

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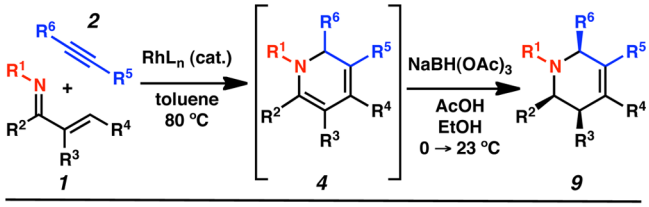
investigated as suitable inputs. Isopropyl methyl acetylene afforded a 2:1 mixture of dihydropyridine regioisomers that underwent protonation and reduction with high diastereoselectivity to give **18** after removal of the minor regioisomer. In contrast, *tert*-butyl methyl acetylene yielded a single dihydropyridine regioisomer, but a mixture of diastereoisomers **19** was obtained after reduction. An unsymmetrical alkyne bearing an amide functionality yielded tetrahydropyridine **20** in 73% yield.[12] Additionally, tetrahydropyridines with appended heterocycles, including furyl **22**–**23**, pyrrolyl **24**, and indolyl **25**, were synthesized in good yields and with excellent diastereoselectivities.

As described in a separate article in this issue, further optimization of this reaction sequence has been carried out for the preparative scale synthesis of tetrahydropyridines (Scheme 1). Using only 0.25 mol % of $[RhCl(coe)_2]_2$, tetrahydropyridines **14** and **22** have been obtained in high overall yields on from 5 to >100 mmol scale. Moreover, the completely air-stable and robust precatalyst $[RhCl(cod)]_2$ can easily be employed for straightforward benchtop set up at only slightly higher catalyst loading and provides the tetrahydropyridine products in comparable yield to that observed for the more active precatalyst $[RhCl(coe)_2]_2$.

Scheme 1. Preparative scale synthesis of tetrahydropyridines



Glovebox set up with 0.25 mol % of $[RhCl(coe)_2]_2$ on >5 mmol scale	14, 87%	22, 80%
Glovebox set up with 0.25 mol % of $[RhCl(coe)_2]_2$ on >100 mmol scale	14, 95%	
Bench top set up with 1 mol % of $[RhCl(cod)]_2$ on >5 mmol scale	14, 82%	22, 83%
Bench top set up with 1 mol % of $[RhCl(cod)]_2$ on >100 mmol scale	14, 93%	

The aforementioned coupling of imines and internal alkynes yielded various structurally unique tetrahydropyridines in excellent yields and diastereoselectivities. Terminal alkynes would also be attractive coupling partners. However, under the conditions for the Rh(I)-catalyzed cascade, terminal alkynes undergo competitive homocoupling.[4b] Silyl alkynes were therefore examined as readily available terminal alkyne surrogates (Table 2).[4b] Treatment of imines **1** with TMS alkynes **26** under the Rh(I)-catalyzed cascade sequence afforded silyl dihydropyridines **27**. Subsequent protonation/reduction of the silyl dihydropyridines **27** led to concomitant removal of the trimethylsilyl group to yield tetrahydropyridines **30**.

A wide range of TMS alkynes were effective substrates for this reaction sequence to provide tetrahydropyridines in high overall yields and with high regio- and diastereoselectivities (Table 2).[4b] As for internal alkyne inputs, the protonation/reduction sequence was performed directly upon the 1,2-dihydropyridine intermediates without isolation. Both electron-rich and -poor aromatic as well as heteroaromatic TMS alkynes were competent in the reaction sequence (**31**–**34**). Alkyl TMS alkynes were also effective inputs (**35**–**39**, **44**). Notably, a variety of functionality could be introduced by the TMS alkyne input to provide a functional group handle for further elaboration (**37**–**39**). Bicyclic tetrahydropyridines could also be constructed in good yield and with high diastereoselectivity (**43**–**46**). Imines with heteroaryl substituents are also suitable precursors as demonstrated for tetrahydropyridines **42** and **48**. Additionally, tetrahydropyridines **47** and **48** with lower levels of substitution can also be prepared using imines without substitution at positions R^2–R^4.

Optimized conditions have also been developed for the preparative scale reaction sequence with TMS alkynes (Scheme 2). The synthesis of tetrahydropyridine **34** was achieved on >5 mmol scale in a high overall yield with only a slight excess of the TMS alkyne (1.2 equiv) and with 0.5 mol % of $[RhCl(coe)_2]_2$ or 1.5 mol % of $[RhCl(cod)]_2$ as the air-stable precatalyst.

Various nucleophiles, besides hydride, have also been added to iminium intermediate **49** (Table 3).[4d] Additions of organometallic reagents such as alkyllithiums and alkyl Grignard reagents resulted in competitive deprotonation to give dihydropyridine **4**. However, by using stabilized organometallic reagents, clean 1,2-nucleophilic addition predominates over undesired deprotonation. For the addition of stabilized organometallic reagents, the dihydropyridines **4** were purified by filtration through alumina prior to the protonation and nucleophilic addition steps, which then proceeded in excellent yields and with high diastereoselectivities. Tetrahydropyridines **51** and **52** were accessed in high yield by the 1,2-addition with allyl and benzyl cerium reagents, respectively. Alkynyl groups were introduced by the addition of alkynyl Grignard reagents to provide **53**, **54**, and **56**. Lastly, tetrahydropyridines with ester substituents **55** and **57** were generated in excellent yield and diastereoselectivity by the addition of Reformatsky zinc enolates.

Carbon electrophiles can also be utilized instead of a proton to provide iminiums under kinetic control with concomitant introduction of an adjacent quaternary carbon (Table 4).[4a] As shown for tetrahydropyridines **59**–**64**, a variety of alkylating agents can be introduced using either alkyl triflates or benzyl chloride with activation by the Lewis acid zinc chloride. Good to outstanding alkylation stereoselectivity was observed when the alkylating agent introduced a quaternary stereocenter, with addition occurring opposite the preexisting R^6 substituent (**60**, **61**, **63**, and **64**). The alkylation stereoselectivity is most clearly distinguished for these products, which were derived from dihydropyridines **4** without substitution at R^2, because reduction does not introduce an additional stereocenter in the tetrahydropyridine products.

Dihydropyridines with substituents at R^2 result in a stereogenic center upon reduction. Ketiminium reduction occurred with high selectivity opposite the R^6 substituent for those dihydropyridines that upon methylation resulted in gem-dimethyl substitution (**65**–**70**). However, when alkylation introduced a quaternary carbon stereocenter adjacent to the formed ketiminium, this proximal stereocenter controlled the

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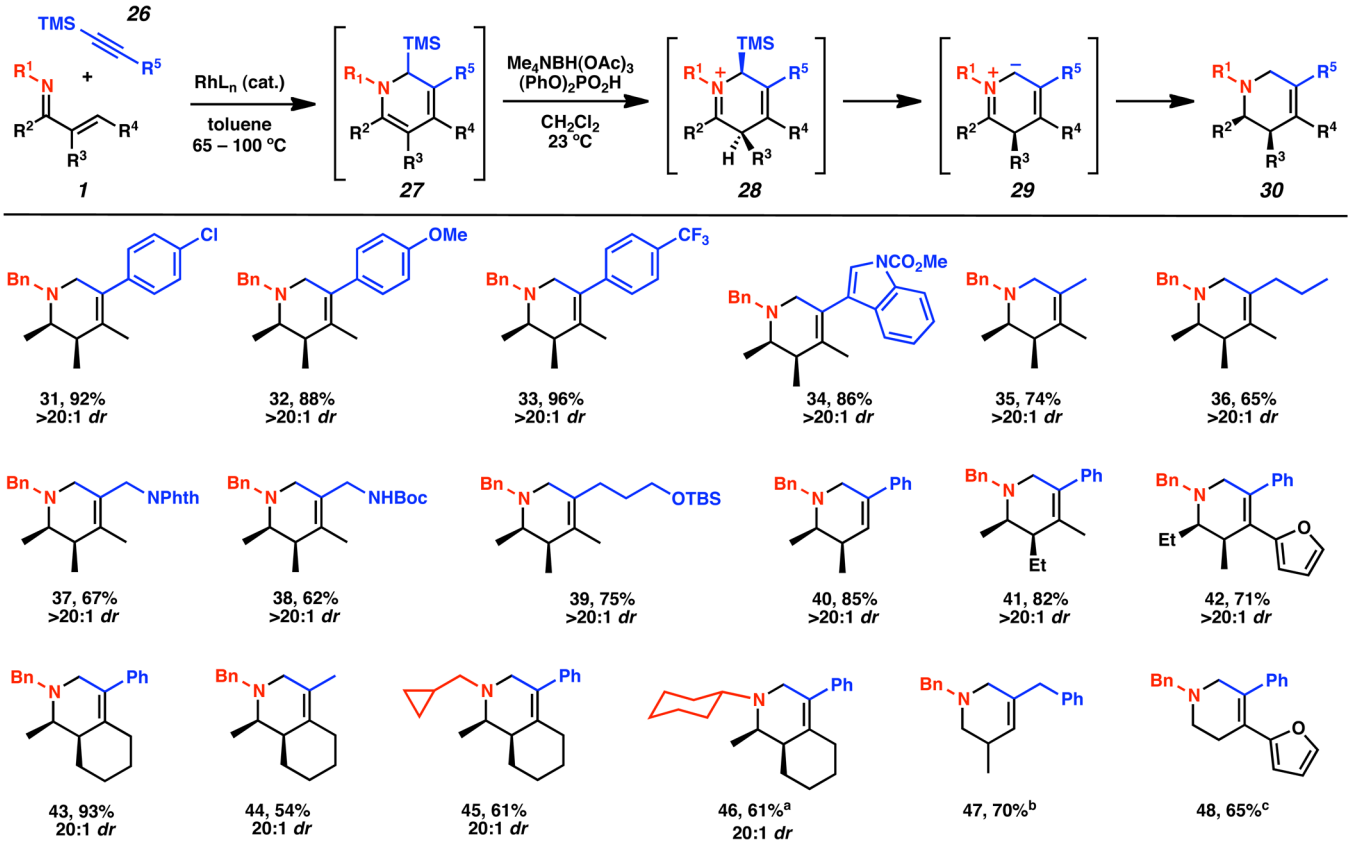
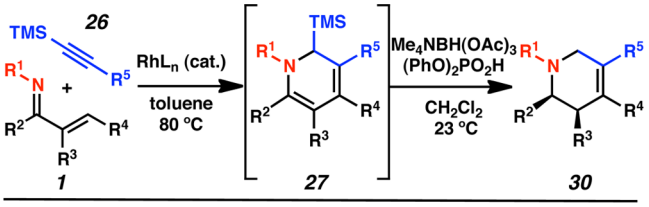
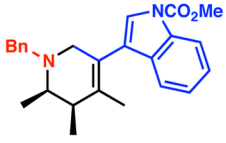
Table 2. Rh-catalyzed cyclization using silyl alkynes with kinetic protonation and reduction



[a]Rh cyclization performed at 65 °C for 16 h and then at 125 °C for 12 h. [b]Reduction performed with $Me_4NBH(OAc)_3$ and HF-pyr in THF at 0 → 23 °C. [c]Reduction performed with HF-pyr and $(PhO)_2PO_2H$ in THF at 0 → 23 °C.

Scheme 2. Preparative scale synthesis of tetrahydropyridines using a silyl alkyne



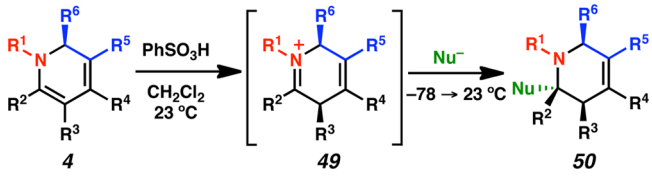


Glovebox set up with 0.5 mol % of $[RhCl(coe)_2]_2$ on >5 mmol scale	34, 86%
Bench top set up with 1.5 mol % of $[RhCl(cod)]_2$ on >5 mmol scale	34, 83%

face selectivity for reduction to override the R^6 substituent (**71**–**76**).

In place of alkylating agents, the Michael acceptor methyl acrylate was also explored as an electrophile to introduce ester functionality (Table 4).[4a] TMSOTf was a necessary activating agent for Michael addition, and under these conditions, the Michael addition and reduction sequence provided products **78** and **77** for dihydropyridines with and without carbon substitution at R^2, respectively.

Table 3. Kinetic protonation and carbon nucleophile addition products



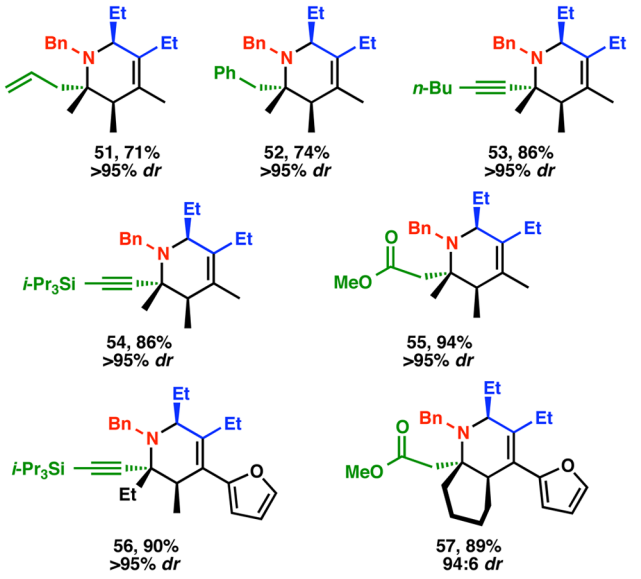


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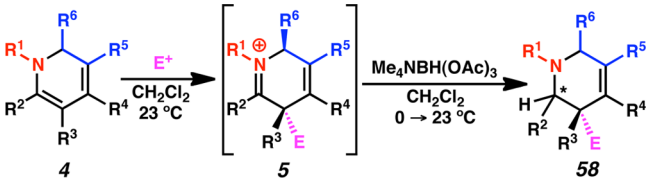
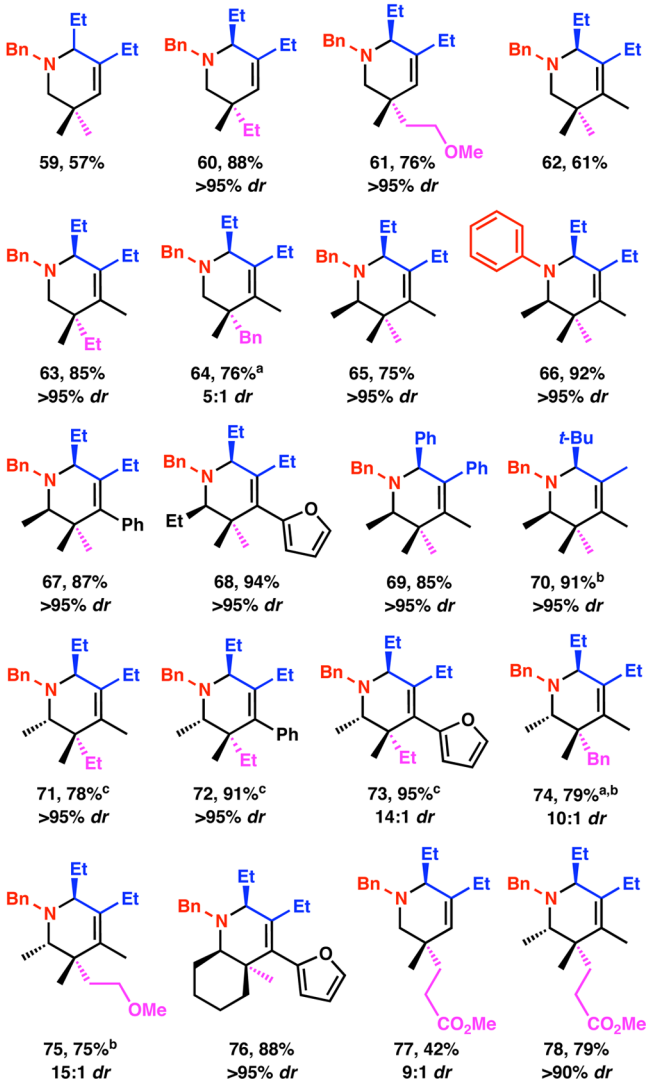
Table 4. Tetrahydropyridines generated via kinetic iminiums from carbon electrophile addition and subsequent reduction

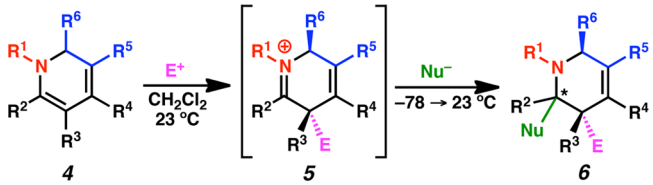


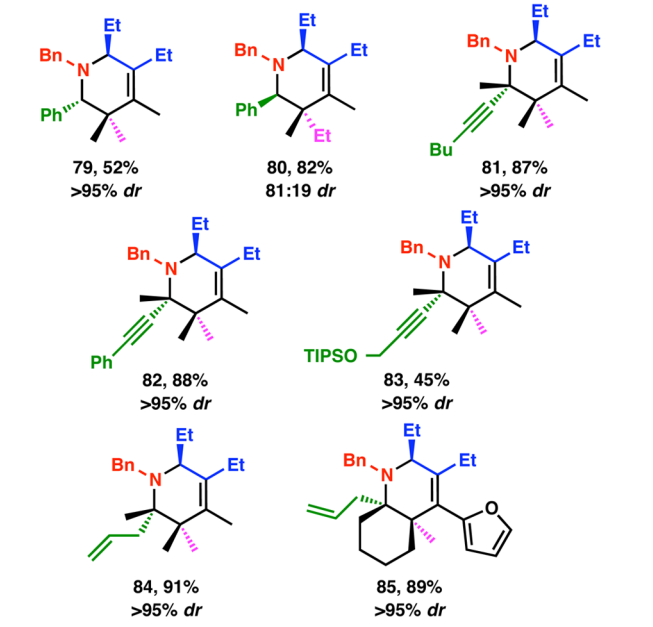


[a]Benzylation occurred with BnBr (2.5 equiv) and $ZrCl_4$ (1.7 equiv) with warming to 23 °C. [b]Reduction was performed by addition of K(*i*-PrO)$_3$BH in THF at −78 °C with warming to 23 °C. [c]Reduction was performed by addition of $LiEt_3BH$ in THF at 78 °C with warming to 23 °C.

Carbon electrophiles combined with carbon nucleophiles have also been employed in the synthesis of densely substituted tetrahydropyridines (Table 5).[4a] Methylation and ethylation of dihydropyridine **4** without substitution at R^2 was followed by addition of phenyl Grignard reagent to give tetrahydropyridines **79** and **80**, respectively. The stereoselectivity at the R^2 position is consistent with that previously observed for ketiminium reduction (vide infra). For an alkylation and carbon nucleophile addition sequence for 1,2-dihydropyridines with carbon substitution at R^2, contiguous tetrasubstituted carbons are generated. Both alkynyl Grignard reagents and allyl cerium

Table 5. Addition of carbon electrophiles and carbon nucleophiles under kinetic control





reagents provided high overall yields for the sequence with excellent diastereoselectivity (**81**−**85**).

PIPERIDINES SYNTHESIZED FROM THERMODYNAMIC IMINIUM INTERMEDIATES

We also developed conditions for the reversible protonation of 1,2-dihydropyridines to provide access to the more thermodynamically stable iminiums, which upon nucleophilic addition would give tetrahydropyridines with a different display of functionality relative to that observed for the corresponding kinetic iminium intermediates (Table 6).[4d] To form the thermodynamic iminium **86**, dihydropyridine **4** must be treated with an acid that is sufficiently weak that it allows equilibration to occur, but that is also sufficiently acidic that at equilibrium the thermodynamic iminium predominates over the starting dihydropyridine. Diphenyl phosphoric acid has the appropriate pK_a and, conveniently, is a free-flowing solid that is not hygroscopic. Treatment of dihydropyridine **4** with two equivalents of diphenyl phosphoric acid for 12−16 h at room temperature provides the thermodynamic iminium **86**, which upon reduction with $Me_4NBH(OAc)_3$ yields the desired tetrahydropyridine **87** (Table 6). For tetrahydropyridines **87** prepared via the thermodynamic iminium intermediate, it is noteworthy that R^5 and R^6 are now trans rather than cis as was observed for the kinetic iminium pathway. This stereochemical outcome is due to the greater stability of the trans versus cis display of these substituents in iminium intermediate **86** as supported by DFT calculations.[4d] Reduction then proceeds with high diastereoselectivity with attack from the opposite face of the R^5 substituent. The thermodynamic protonation/reduction sequence proceeds with comparable scope to that

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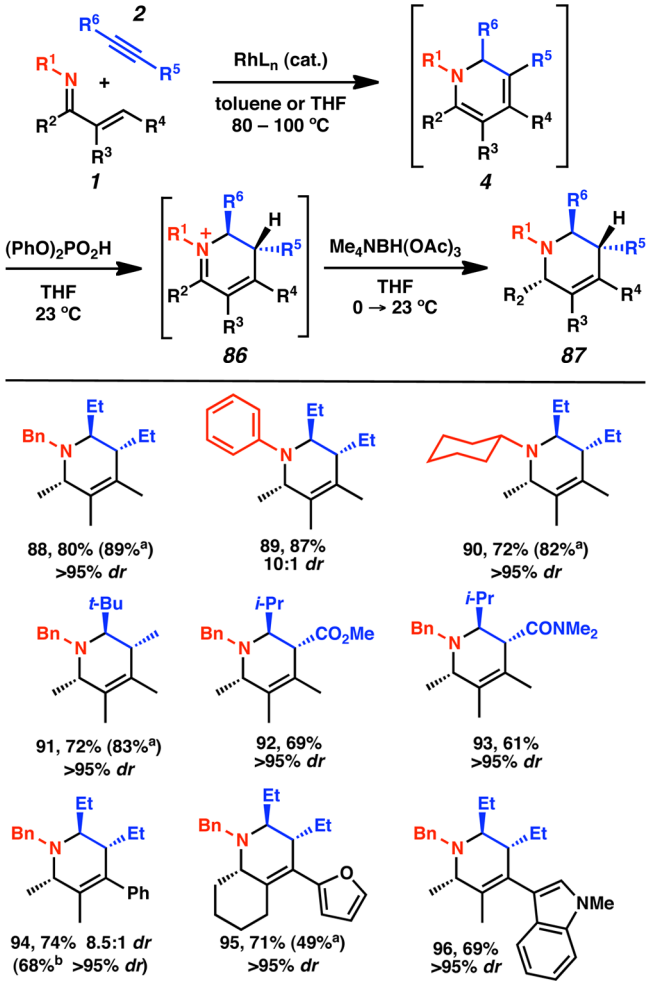
Table 6. Thermodynamic protonation and reduction tetrahydropyridine products

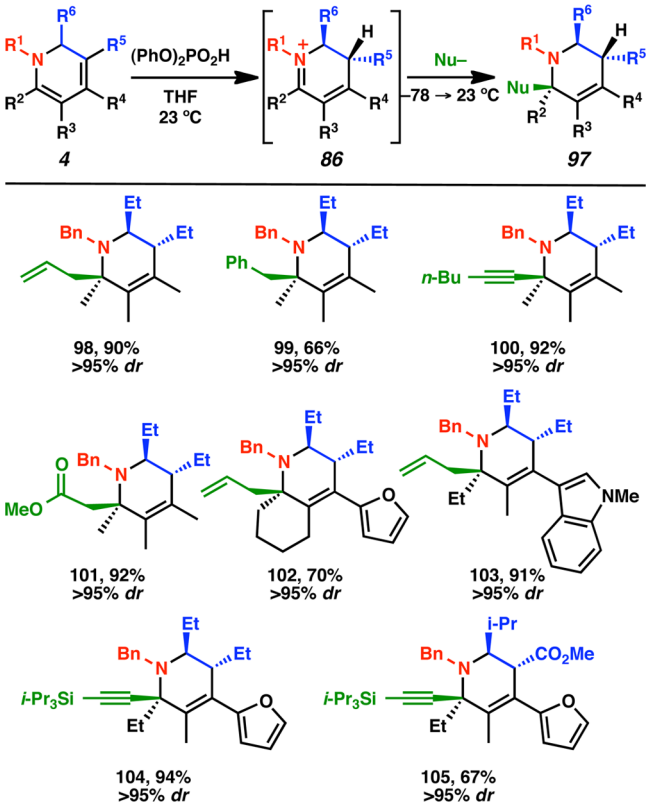


[a][Rh] step run in THF, and the reaction is carried out as a onepot procedure. [b][Rh] step run in THF, and reduction conducted using Li[*i*-Bu_3BH].

observed for the kinetic protonation/reduction sequence. A variety of *N*-substituents are compatible with this sequence, including benzyl, aryl, and branched alkyl groups. The use of 1,2-dihydropyridines prepared from unsymmetrical alkynes as coupling partners afforded products **91**–**93** in good yield and with excellent diastereoselectivity. Bicyclic tetrahydropyridines can also be prepared, as exemplified by tetrahydropyridine **95**, and the sequence is compatible with the introduction of oxygen and nitrogen heteroaromatic substituents (**95** and **96**).

In addition to the reduction of the thermodynamic iminium intermediate, carbon-based nucleophiles can also be added (Table 7).[4d] Allyl cerium reagents furnished tetrahydropyridines **98**, **102**, and **103**, and a benzyl cerium reagent provided tetrahydropyridine **99**. Alkynyl substituents were incorporated to yield densely substituted products **100**, **104**, and **105**, including the tetrahydropyridines **104** and **105** bearing silyl functionality. Reformatsky enolate addition provided tetrahydropyridine **101**. All of the products were obtained with excellent diastereoselectivity and in good to high yields based upon the 1,2-dihydropyridine, which had been isolated by filtration through alumina.

Table 7. Thermodynamic protonation with carbon nucleophile addition products



BRIDGED BICYCLICS

1,2-Dihydropyridines are versatile synthetic intermediates for the preparation of bridged bicyclic systems. For example, 1,2-dihydropyridines have served as electron-rich dienes for Diels–Alder cycloadditions to generate isoquinuclidines,[13] which are present in alkaloid natural products and bioactive drug candidates. However, dihydropyridines with high substitution levels such as those that can be readily generated by the Rh-catalyzed C–H bond activation/alkenylation/electrocyclization cascade had not been previously investigated, and therefore, dienophiles with varying reactivity were evaluated (Table 8).[4c] The highly electron deficient dienophile, *N*-phenylmaleimide, underwent smooth cycloaddition at room temperature to yield isoquinuclidine **108** as a single regioisomer and exclusively as the endo stereoisomer. For the less reactive dienophiles, methyl acrylate and acrylonitrile, heating the dihydropyridine neat with excess dienophile at 105 °C was necessary to achieve high yields of isoquinuclidines **109** and **110**, respectively. For cycloaddition with crotonaldehyde, the Lewis acid zinc chloride was employed to furnish product **111** in 65% yield. The substituent at the *N*-position was also examined with benzyl, aryl, and branched alkyl groups all providing cycloaddition products **108**–**123**. Isoquinuclidines **121**–**123** were also prepared from dihydropyridines without substitution at one or more of the sites R^2–R^4.

In the context of employing silyl alkynes as terminal alkyne surrogates for the Rh-catalyzed activation/alkenylation/electrocyclization cascade for tetrahydropyridine synthesis, we discovered that loss of the trimethylsilyl group proceeds via an unstabilized azomethine ylide intermediate **29** (Table 9).[4b] Unstabilized ylides, particularly with this level of complexity, are not straightforward to prepare, and therefore we sought to

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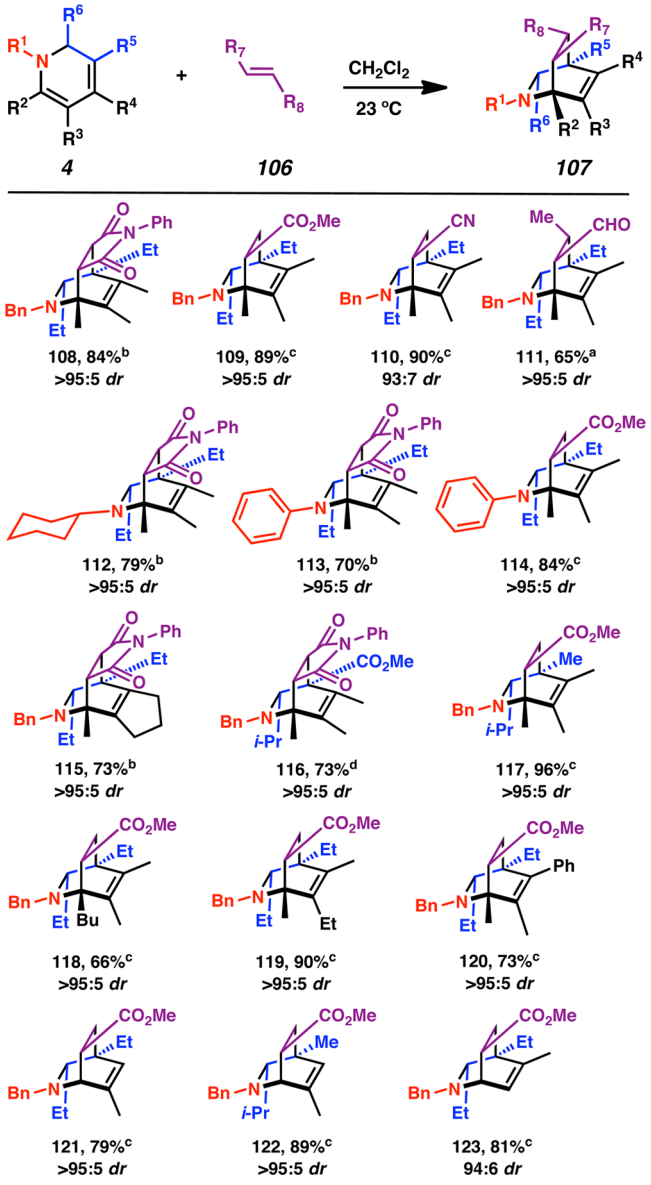
Table 8. Diels–Alder cycloaddition of 1,2-dihydropyridines



[a]$ZnCl_2$ (1.1 equiv), 0 °C. [b]*N*-Phenylmaleimide (1.05 equiv), 23 °C. [c]Neat, 105 °C. [d]*N*-Phenylmaleimide (1.05 equiv), 50 °C.

leverage this new protonation and desilylation approach to access these reactive dipoles for the synthesis of highly substituted tropanes **125** (Table 9). Although a large number of examples of pyrrolidine synthesis via [3 + 2] dipolar cycloaddition of azomethine ylides have been disclosed,[14] few examples to tropanes have been reported.[15] A variety of substituents could be incorporated, including alkyl and aryl groups at positions R^2 to R^5 as well as without substitution at positions R^2 to R^4. In all cases, high face selectivity was observed with reaction of the dipolarophile opposite the R^3 group. When the unsymmetrical dipolarophile, methyl propiolate, was employed, a mixture of regioisomers were obtained that were separable by silica gel chromatography (**131** and **132**).

While investigating the treatment of silyl dihydropyridine with acids of different strength, an unexpected product was obtained (Figure 4).[4b] The addition of benzenesulfonic acid to dihydropyridine **135** at −78 °C afforded cyclopropyl

Table 9. Tropane synthesis via azomethine ylides

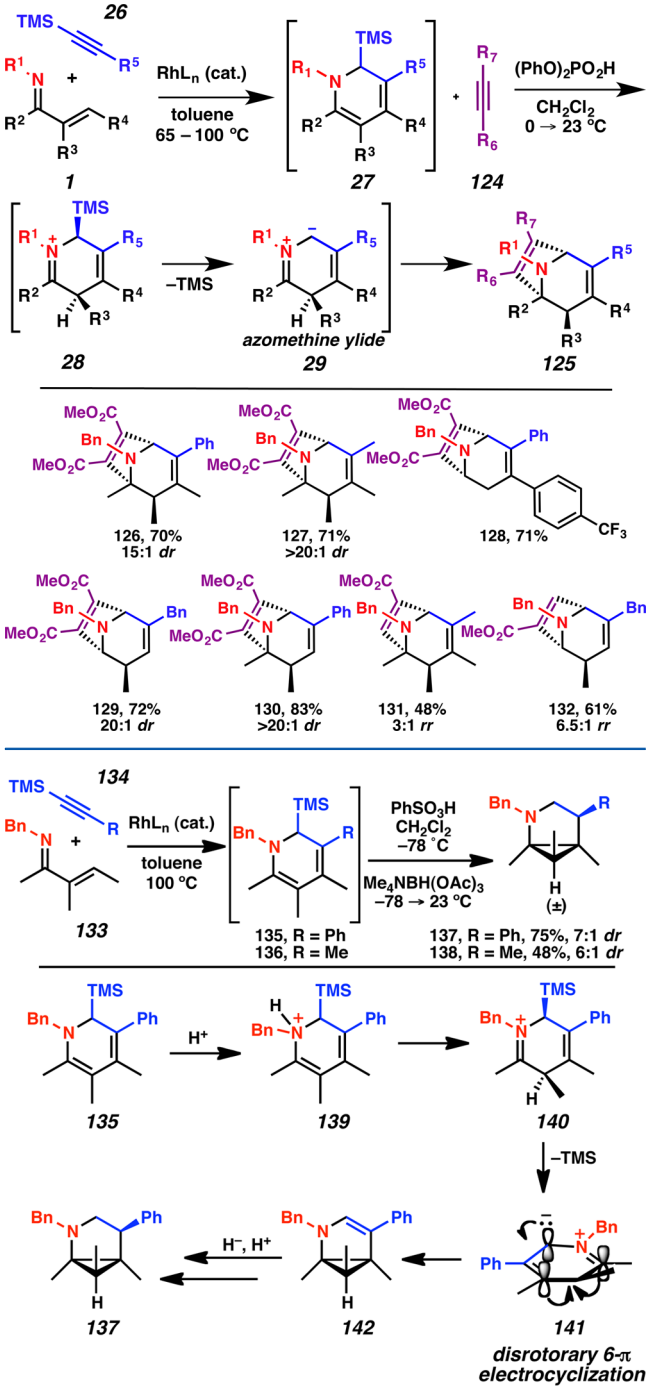


Figure 4. Synthesis of cyclopropyl pyrrolidines.

pyrrolidine **137**. The identity of this product was confirmed via X-ray crystallography of its hydrochloride salt.[4b] Although a 75% yield was obtained for the cyclopropyl pyrrolidine **137** with R = Ph, a diminished 48% yield of **138** was observed when the phenyl group was replaced by a methyl group. We believe that the cyclopropyl pyrrolidine products are the result of a disrotary 6π-electrocyclization of iminium **141** (Figure 4).

CONCLUSION

In conclusion, we have reported a Rh-catalyzed C–H bond activation/alkenylation/electrocyclization cascade to provide

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diverse 1,2-dihydropyridines from simple and readily available precursors. These useful synthetic intermediates add to proton and carbon electrophiles under kinetic or thermodynamic conditions to yield a wide range of iminiums. Subsequent addition of a nucleophile generates a diverse array of piperidine products. Additionally, [3 + 2] and [4 + 2] cycloadditions of the 1,2-dihydropyridine intermediates provides access to bridged bicyclic structures such as tropanes and isoquinuclidines. This concise reaction sequence enables the formation of highly substituted piperidines in synthetically useful yields with excellent diastereoselectivity.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For an analysis of the prevalence of piperidines in drug discovery, see Table 6 and Figure 1 in: Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451.

(2) The piperidine structural properties are consistent with the development of drug candidates having increased saturation. See: (a) Walters, W. P.; Green, J.; Weiss, J. R.; Murcko, M. A. *J. Med. Chem.* **2011**, *54*, 6405. (b) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752. (c) Ritche, T. J.; Macdonald, S. J. F. *Drug Discovery Today* **2009**, *14*, 1011.

(3) For general reviews on piperidines, see: (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139. (b) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (c) Mitchenson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862. (d) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781.

(4) (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.; Wiberg, K. B.; Bergman, R. G.; Ellman, J. A. *Science* **2013**, *339*, 678. (e) Duttwyler, S.; Lu, C.; Rheingold, A. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 4064.

(5) For reviews on the synthesis and applications of 1,2-dihydropyridines, see: (a) Silva, E. M. P.; Varandas, P. A. M. M.; Silva, A. M. S. *Synthesis* **2013**, 3053. (b) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642. (c) Tanaka, K.; Fukase, K.; Katsumura, S. *Synlett* **2011**, 2115.

(6) For recent methods for the synthesis of 1,2-dihydropyridines, see: (a) Mizoguchi, H.; Oikawa, H.; Oguri, H. *Nat. Chem.* **2014**, *6*, 57. (b) Chau, S. T.; Lutz, J. P.; Wu, K.; Doyle, A. G. *Angew. Chem., Int. Ed.* **2013**, *52*, 9153. (c) Yamakawa, T.; Yoshikai, N. *Org. Lett.* **2013**, *15*, 196. (d) Amatore, M.; Leboeuf, D.; Malacria, M.; Gandon, V.; Aubert, C. *J. Am. Chem. Soc.* **2013**, *135*, 4576. (e) Oshima, K.; Ohmura, T.; Suginome, M. *J. Am. Chem. Soc.* **2012**, *134*, 3699. (f) Nadeau, C.; Aly, S.; Belyk, K. *J. Am. Chem. Soc.* **2011**, *133*, 2878. (g) Jarvis, S. B. D.; Charette, A. B. *Org. Lett.* **2011**, *13*, 3830.

(7) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 5604.

(8) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645.

(9) For leading references on alternative syntheses of pyridines via C−H activation, see: (a) Zhang, Q.-R.; Huang, J.-R.; Zhang, W.; Dong, L. *Org. Lett.* **2014**, *16*, 1684. (b) Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 66. (c) Martin, R. M.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2012**, *77*, 2501. (d) Too, P. C.; Noji, T.; Lim, Y. J.; Li, X.; Chiba, S. *Synlett* **2011**, 2789. (e) Hyster, T. K.; Rovis, T. *Chem. Commun.* **2011**, *47*, 11846. (f) Parthasarathy, K.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2008**, *10*, 325.

(10) For reviews on tetrahydropyridines, see: (a) Mateeva, N. N.; Winfield, L. L.; Redda, K. K. *Curr. Med. Chem.* **2005**, *12*, 551. (b) Felpin, F. X.; Lebreton, J. *Curr. Org. Synth.* **2004**, *1*, 83.

(11) For select recent methods for the preparation of highly substituted tetrahydropyridines, see: (a) Martin, T. J.; Rovis, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 5368. (b) Shi, F.; Tan, W.; Zhou, R.-Y.; Xing, G.-J.; Tu, S.-J. *Adv. Synth. Catal.* **2013**, *355*, 1605. (c) Li, X.; Zhao, Y.; Qu, H.; Mao, Z.; Lin, X. *Chem. Commun.* **2013**, *49*, 1401. (d) Lemonnier, G.; Charette, A. B. *J. Org. Chem.* **2012**, *77*, 5832. (e) Yang, D. X.; Micalizio, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 15237. (f) Harrison, D. P.; Iovan, D. A.; Myers, W. H.; Sabat, M.; Wang, S. S.; Zottig, V. E.; Harman, W. D. *J. Am. Chem. Soc.* **2011**, *133*, 18378.

(12) See ref 4d, Supporting Information.

(13) For select examples of the preparation of isoquinuclidines from *N*-alkyl 1,2-dihydropyridines and alkenes, see: (a) Taylor, S. J.; Taylor, A. M.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1681. (b) Reine, I.; Muceniece, V. L.; Kemme, A. *Heterocycl. Commun.* **2002**, *8*, 173. (c) dos Santos, D. C.; de Freitas Gil, R. P.; Gil, L.; Marazano, C. *Tetrahedron Lett.* **2001**, *42*, 6109. (d) Mehmandoust, M.; Marazano, C.; Singh, R.; Gillet, B.; Césario, M.; Fourrey, J.-L.; Das, B. C. *Tetrahedron Lett.* **1988**, *29*, 4423. (e) Cardellini, M.; Cingolani, G. M.; Claudi, F.; Gulini, U.; Cantalamessa, F.; Venturi, F. *Eur. J. Med. Chem.* **1987**, *22*, 1.

(14) For reviews on [3 + 2]-azomethine ylide dipolar cycloadditions, see: (a) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484. (b) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765. (c) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.

(15) (a) Pandey, G.; Laha, J. K.; Lakshmaiah, G. *Tetrahedron* **2002**, *58*, 3525. (b) Pandey, G.; Sahoo, A. K.; Bagul, T. D. *Org. Lett.* **2000**, *2*, 2299. (c) Pandey, G.; Laha, J. K.; Mohanakrishnan, A. K. *Tetrahedron Lett.* **1999**, *40*, 6065. (d) Pandey, G.; Lakshmaiah, G.; Ghatak, A. *Tetrahedron Lett.* **1993**, *34*, 7301.