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). 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. This approach is centered upon a Rh-catalyzed C–H activation/alkenylation/electrocyclization cascade to provide 1,2-dihydropyridines (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 diastereoselectivity. In this review, we survey the diversity of structures that can be accessed by this approach. 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). Using [RhCl(coe)]₂ (coe = cyclooctene) as the precatalyst and the now commercially available 4-(diethylphosphino)-N,N-dimethylalanine 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). 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.

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). 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). Nucleophilic attack would then provide tetrahydropyridine 8. Additional transformations of 1,2-dihydropyridine 4 to provide bridged bicyclic products are also possible (vide infra).

PIPERIDINES SYNTHESIZED FROM KINETIC IMINUIM INTERMEDIATES

Our initial demonstration of this approach proceeded by the stereoselective protonation and in situ reduction of the resulting kinetically formed iminium 5. 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. 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 R₂ substituent blocks one face of the dihydropyridine as a result of its pseudoaxial display enforced by A-1,2-strain. Reduction then proceeds from the face opposite both
the R6 and the R2 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 R2−R4 of imine 1 (Table 1). 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 NN-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 |
|---|
| ![Diagram of reaction](image) |
| ![Diagram of compounds](image) |

"Alkyne regioselectivity 2:1; combined yield for separate regioisomers. "Combined yield for regioisomERICALLY pure diastereomERIC mixture.
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. 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 1 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)]\(_2\).

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(1)-catalyzed cascade, terminal alkynes undergo competitive homocoupling. Silyl alkynes were therefore examined as readily available terminal alkyne surrogates (Table 2). Treatment of imines 1 with TMS alkynes 26 under the Rh(1)-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). 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)]\(_2\) 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). Additions of organometallic reagents such as alkylolithiums 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 benzylic cerium reagents, respectively. Alkynyl groups were introduced by the addition of allyl 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). As shown for tetrahydropyridines 59−64, a variety of alkylating agents can be introduced using either alkyl triflates or benzylic 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\(^2\) 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
face selectivity for reduction to override the R6 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 R2, respectively.

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

| R1  | R2 | R3  | R4 | Product 78 or 77 | Yield |
|-----|----|-----|----|-----------------|-------|
| Cl  | H  | OMe | H  | 32              | 88%   |
| CF3 | H  | H   | H  | 33              | 96%   |
| NCOO Me | H | H   | H  | 34              | 86%   |
| NPhth | H | H   | H  | 35              | 74%   |
| NPh | H  | H   | H  | 36              | 65%   |

| R1  | R2 | R3  | R4 | Product 78 or 77 | Yield |
|-----|----|-----|----|-----------------|-------|
| Ph  | H  | H   | H  | 37              | 67%   |
| Ph  | H  | H   | H  | 38              | 62%   |
| Ph  | H  | H   | H  | 39              | 75%   |
| Ph  | H  | H   | H  | 40              | 85%   |
| Ph  | H  | H   | H  | 41              | 82%   |
| Ph  | H  | H   | H  | 42              | 71%   |

| R1  | R2 | R3  | R4 | Product 78 or 77 | Yield |
|-----|----|-----|----|-----------------|-------|
| Ph  | H  | H   | H  | 43              | 93%   |
| Ph  | H  | H   | H  | 44              | 54%   |
| Ph  | H  | H   | H  | 45              | 61%   |
| Ph  | H  | H   | H  | 46              | 61%   |
| Ph  | H  | H   | H  | 47              | 70%   |
| Ph  | H  | H   | H  | 48              | 65%   |

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

Table 3. Kinetic protonation and carbon nucleophile addition products

| R1  | R2 | R3  | R4 | Product 49 or 50 | Yield |
|-----|----|-----|----|-----------------|-------|
| Ph  | H  | H   | H  | 51              | 71%   |
| Ph  | H  | H   | H  | 52              | 74%   |
| Ph  | H  | H   | H  | 53              | 86%   |
| Ph  | H  | H   | H  | 54              | 86%   |
| Ph  | H  | H   | H  | 55              | 94%   |
| Ph  | H  | H   | H  | 56              | 90%   |
| Ph  | H  | H   | H  | 57              | 89%   |
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 R2 was followed by addition of phenyl Grignard reagent to give tetrahydropyridines 79 and 80, respectively. The stereoselectivity at the R2 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 R2, contiguous tetrasubstituted carbons are generated. Both alkynyl Grignard reagents and allyl cerium 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 pKₐ 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 Me₄NBH(OAc)₃ yields the desired tetrahydropyridine 87 (Table 6). For tetrahydropyridines 87 prepared via the thermodynamic iminium intermediate, it is noteworthy that R5 and R6 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 R5 substituent. The thermodynamic protonation/reduction sequence proceeds with comparable scope to that...
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). Allyl cerium reagents furnished tetrahydropyrindines 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 tetrahydropyrindines 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.

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**Table 6. Thermodynamic protonation and reduction tetrahydropyridine products**

| R<sup>1</sup> | R<sup>2</sup> | R<sup>3</sup> | R<sup>4</sup> |
|------------|------------|------------|------------|
| R<sup>5</sup> | R<sup>6</sup> | R<sup>7</sup> | R<sup>8</sup> |
| 86 | (PhO)<sub>2</sub>POH |
| THF 23 °C |
| Me<sub>2</sub>NBH(OAc)<sub>2</sub> | THF 0–23 °C |

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**Table 7. Thermodynamic protonation with carbon nucleophile addition products**

| Nu<sup>−</sup> | R<sup>1</sup> | R<sup>2</sup> | R<sup>3</sup> | R<sup>4</sup> |
|------------|------------|------------|------------|------------|
| Li[Bu<sub>3</sub>BH] |

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**BRIDGED BICYCLES**

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, 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).

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<sup>2</sup>–R<sup>4</sup>.

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). Unstabilized ylides, particularly with this level of complexity, are not straightforward to prepare, and therefore we sought to...
leverage this new protonation and desilylation approach to access these reactive dipoles for the synthesis of highly substituted tropanes (Table 9). Although a large number of examples of pyrrolidine synthesis via [3 + 2] dipolar cycloaddition of azomethine ylides have been disclosed, few examples to tropanes have been reported. A variety of substituents could be incorporated, including alkyl and aryl groups at positions R2 to R5 as well as without substitution at positions R2 to R4. In all cases, high face selectivity was observed with reaction of the dipolarophile opposite the R3 group. When the unsymmetrical dipolarophile, methyl propioloate, 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). The addition of benzenesulfonic acid to dihydropyridine 135 at −78 °C afforded cyclopropyl pyrrolidine 137. The identity of this product was confirmed via X-ray crystallography of its hydrochloride salt. 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 disrotatory 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...
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 isoquinuclides. 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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