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Proton Donor Acidity Controls Selectivity in Nonaromatic Nitrogen Heterocycle Synthesis

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Abstract

Piperidines are prevalent in natural products and pharmaceutical agents and are important synthetic targets for drug discovery and development. We report a methodology that provides highly substituted piperidine derivatives with regiochemistry selectively tunable by varying the strength of acid used in the reaction. Readily available starting materials are first converted to dihydropyridines via a cascade reaction initiated by rhodium-catalyzed C–H bond activation. Subsequent divergent regio- and diastereoselective protonation of the dihydropyridines under either kinetic or thermodynamic control provides two distinct iminium ion intermediates that then undergo highly diastereoselective nucleophilic additions. X-ray structural characterization of both the kinetically and thermodynamically favored iminium ions along with density functional theory calculations provide a theoretical underpinning for the high selectivities achieved for the reaction sequences.

Piperidines are saturated, non-planar nitrogen heterocycles upon which the display of functionality has provided some of the most well known pharmaceuticals as exemplified by traditional drugs such as quinine, morphine and its many synthetic analogues such as oxycodone, as well as a number of more recent blockbusters including plavix for the treatment of stroke, cialis for erectile dysfunction, and aricept for Alzheimer's treatment (Fig. 1A) (1). The physical properties and therapeutic importance of the piperidine scaffold are consistent with recent retrospective analyses of drug discovery research suggesting that renewed emphasis should be placed on the preparation, evaluation and development of compounds with increased saturation and non-planar display of functionality (2–4).

C–H bond functionalization has emerged as a powerful approach for the synthesis and modification of planar, aromatic *N*-heterocycles from cheap and readily available precursors (5–11). Recently we reported a cascade reaction comprising rhodium-catalyzed C–H activation of imines **1** with coupling to alkynes **2** to give azatrienes **3** followed by electrocyclization to provide densely substituted 1,2-dihydropyridines **4** (Figure 1B) (12, 13–15). These relatively unstable non-aromatic *N*-heterocycles can readily be aromatized to stable pyridines. Dihydropyridines **4** can also be converted to more highly saturated heterocycles (16); however, highly substituted derivatives have previously been difficult to

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Metrical parameters for the structures of compounds **5a**, **6a**, **7p**, **8a**, and **8m** are available free of charge from the Cambridge Crystallographic Data Centre under reference numbers CCDC- xxx-xxx, respectively.

Supplementary Materials:

Materials and methods

access and pose a particular challenge in terms of regio- and stereochemical transformation. Recently, we demonstrated an in situ protonation/reduction sequence that provides tetrahydropyridines **7** with very high regio- and diastereoselectivity (17). Here we demonstrate that tetrahydropyridines **8** with an alternative substitution pattern and stereochemical display can be accessed by tuning the strength of the acid used. In addition to hydride, a range of carbon nucleophiles have also been added to both iminium intermediates **5** and **6** to provide even more densely substituted derivatives of **7** and **8**.

Consider the addition of a proton, the simplest of all electrophiles, to highly substituted 1,2-dihydropyridine **4a** (Fig. 2). The four most likely products are *cis* and *trans* stereoisomers of reactive iminium ions **5a** and **6a**, obtained by protonation at the 3- and 4-positions, respectively. Each of these reactive intermediates might also be expected to undergo additional transformations to give undesired byproducts such as enamine tautomers or dimers and higher order oligomers.

Despite the large potential number of products, we directed our efforts at the selective formation of single iminium isomers (18,19). When a strong acid with a pK_a several units below that of **4a** is used, 3-protonation occurs under kinetic control to give **5a** as the major product (Fig. 2). Preferred kinetic protonation at the 3-position is consistent with electrophilic attack reported for conjugated dienolates (20). A screening of acids and solvents showed that arylsulfonic acids in dichloromethane afford 3-protonated *cis*-**5a** as a single diastereomer with >95% selectivity. Thus, treatment of **4a** with 1.1 equivalents of PhSO₃H in dichloromethane at room temperature resulted in complete protonation within 15 min as evidenced by ¹H NMR spectroscopy. Isomerization to other species, eventually *trans*-**6a**, took place over with a half life of 38 hours.

Protonation of **4a** under thermodynamic control was achieved using two equivalents of a weaker acid and equilibration over 12 to 16 h at room temperature. Treatment with (PhO)₂PO₂H in THF at room temperature gave 4-protonated *trans*-**6a** with >95% regio- and diastereochemical purity. Solutions of *trans*-**6a** remained unchanged at room temperature over weeks and upon heating to 80 °C for 1 day, indicating that the thermodynamically most stable ion had formed. From a practical point of view, benzenesulfonic acid and diphenyl phosphoric acid not only permit the directed formation of **5a** and **6a**, but also have the advantage of being easily weighable solids which provide iminium salts that are soluble in organic solvents.

To rigorously define the relative stereochemistry and obtain a better understanding of the conformations of the products of protonation, X-ray structures were obtained for kinetically favored iminium ion *cis*-**5a** and thermodynamically favored iminium ion *trans*-**6a**. Moreover, for kinetic iminium ion *cis*-**5a** a fast crystallization process (2 h) rather than typically preferred slow crystal formation was necessary to prevent iminium equilibration. The ring in kinetic ion *cis*-**5a** adopts a boat-like conformation with the C3-Me and C6-Et substituents in pseudoaxial positions (Fig. 3A1). The piperidine ring in the thermodynamic ion *trans*-**6a** exhibits a more planar geometry of the N-C1-C2-C3 moiety with the C5-Et and C6-Et substituents now disposed in pseudoaxial positions (Fig. 3A2). Presumably, the pseudoaxial orientation of the substituents on the saturated carbons for both the kinetic and thermodynamic iminium ions avoids unfavorable A-1,2-interactions (vide infra).

DFT calculations were carried out at the B3LYP/6-311G+(d,p) level of theory to further characterize the energies and conformations for the four possible protonation products (21). The kinetic iminium ion *cis*-**5a** was calculated to adopt a boat-like conformation with the C3-Me and C6-Et groups in pseudoaxial positions, consistent with the X-ray structure (Figure 3B1). The alternative boat-like conformation with the C3-Me and C6-Et groups in

pseudo-equatorial positions was calculated to be higher in energy by 8.3 kcal/mol, consistent with the unfavorable A-1,2-interactions imparted by adjacent alkenyl methyl groups (22). The thermodynamic protonation product *trans*-**6a** was calculated to be the most stable of the four possible iminium ions by >3 kcal/mol, consistent with it being the only observable isomer under thermodynamic control (Figure 3B2). The overall geometry, bond distances and angles obtained with the DFT calculations are in very good agreement with the structures obtained for both *cis*-**5a** and *trans*-**6a**.

The conditions developed for kinetic and thermodynamic protonation to provide single diastereomers of reactive iminium ions set the stage for an extremely efficient protocol to prepare distinct regio- and diastereomeric tetrahydropyridines **7** and **8** with multiple stereogenic centers. Dihydropyridines **4** are first prepared by the aforementioned Rh-catalyzed cascade process from commercially available alkynes **2** and imines **1**, which are in turn readily prepared from common enones and primary amines. Kinetic protonation of **4** at the α -position provides iminium ions **5**, which upon nucleophilic addition should provide tetrahydropyridines **7**. Alternatively, thermodynamic protonation at the β -position provides ions **6**, to which nucleophilic addition should provide tetrahydropyridines **8**, respectively. Variation of the substitution pattern in each starting component should result in a vast number of potential permutations for the differential display of functionality in the stable piperidine derivatives **7** and **8**.

We first sought to explore reductions to provide hydride addition products **7** and **8** obtained from kinetic and thermodynamic protonation, respectively (Table 1). We recently reported that upon formation of dihydropyridine **4** treatment with Na[(AcO)₃BH] in the presence of acetic acid provides **7** (Nu = H) in good overall yields based upon starting imine **2** with uniformly very high stereoselectivity (17). This reaction presumably proceeded by *in situ* formation and then reduction of kinetic iminium **5**.

To explore reduction of the thermodynamically favored iminiums **6**, Formation of **6a** under thermodynamic control was followed by reduction with the mild hydride donor [(AcO)₃BH][−] in THF to afford tetrahydropyridine **8a** in an 80% overall yield with respect to imine **1a** (Table 1, conditions B/C). Compound **8a** was formed as a single diastereomer as evidenced by NMR spectra of the crude product mixture; its relative configuration of the saturated ring carbon atoms was established unambiguously by X-ray crystallography (Fig. S4). Starting from differently substituted imine and alkyne precursors, products **8b–i** were obtained in high overall yields of 61 to 87% (Table 1). More importantly, very high diastereoselectivities were observed uniformly except for **8b** and **8g**, which were obtained as a 10:1 and 8.5:1 mixture of two diastereomers, respectively. In the case of **8g**, reduction using Li[*i*-Bu₃BH] increased the diastereoselectivity to >95% and showed that improvement of diastereomeric ratio was possible using a sterically more demanding reducing agent. Tolerance of different *N*-substituents (**8a–c**), unsymmetrical and functionalized alkynes (**8d–f**), as well as (hetero-)aryl substituents (**8g–i**) underscored the generality of the methodology.

Through this sequence the piperidine products **8** were obtained via the direct generation of iminium ions **6** from imine and alkyne inputs. Isolation of the dihydropyridine intermediate **4** prior to protonation and reduction was only necessary for the preparation of products **8e** and **8f**. All other highly substituted piperidine derivatives required only a single workup and purification at the end of the sequence.

Successful hydride reduction of the iminium ions suggested the feasibility of diastereoselective addition of carbon nucleophiles, though competitive deprotonation pathways posed a challenge. Iminium ions **5** and **6** both exhibited *C*-electrophilic C2-

positions, but also Brønsted-acidic and sites where protonation of the system of **4** had occurred. Organometallic reagents R–[M] of high Brønsted basicity, such as alkyllithiums and alkyl Grignard reagents, led to mixtures of C2-addition products **7** or **8** and dihydropyridines **4** resulting from deprotonation. We identified several nucleophiles that underwent clean 1,2-addition and afforded only minor amounts of undesired elimination products. Allyl, benzyl, alkynyl, and ester groups could be introduced using allyl–[CeCl₂], ArCH₂–[CeCl₂], RC≡C–[MgCl], and ROC(O)CH₂–[ZnBr] reagents, respectively. Organometallic reagents were selected that favor electrophilic addition over competitive deprotonation pathways (23).

Addition reactions to both *cis*-**5** and *trans*-**6** proceeded in high yields and excellent diastereoselectivities (Table 1). For these transformations, the dihydropyridine intermediates **4** were separated from the rhodium catalyst by filtration through alumina, converted to the iminium ions with PhSO₃H or (PhO)₂PO₂H, and added to an excess of the carbon nucleophile in THF or diethyl ether. Tetrahydropyridines **7a–g** and **8j–q** were obtained in yields of 66 to 94% and with excellent *d*_{rs} of 94:6 or higher. NMR spectra of the crude products confirmed that the diastereoselectivities were not a result of selective isolation of one particular stereoisomer. In analogy to the hydride reductions of **6**, exclusive 1,2-addition (no 1,4-derivatization) was observed. Relative configurations were inferred on the basis of crystal structures of **7a** (**8**), **7e**, and **8m** (Fig. S5 and S6) and the similarities of the NMR spectra of the two sets of products. Compounds **7** exhibited all-*cis* stereochemistry of the substituents R², R³ and R⁶, whereas for **8** *trans*-R⁵/R⁶ and *trans*-R⁶/R² stereochemistry was observed. Thus, the facial selectivity for the addition step was the same for [(AcO)₃BH][–] and the organometallic reagents, suggesting that the preferred trajectory was mainly determined by the geometry of the iminium ions **5** and **6** and to a lesser extent by the nature of the nucleophile. Tetrahydropyridine **8q** features seven different substituents as a result coupling of a differentially substituted imine with an unsymmetrical alkyne and addition of an alkynyl nucleophile. Such a level of directed placement of substituents around a piperidine ring has not been reported to the best of our knowledge (21,22).

The X-ray structures of the reactive iminium ions *cis*-**5a** and *trans*-**6a** offer prospective insight into of the high diastereoselectivities that were consistently observed in the nucleophilic addition steps. Nucleophilic addition to ion *cis*-**5a** is most likely directed by the pseudo-axial C3-substituent, which exerts the strongest steric hindrance to nucleophiles approaching the C2 electrophilic center. The relatively planar C2–C3–C4 moiety of *trans*-**6a** provides little facial steric bias for the incoming nucleophile. We therefore hypothesize that the conformation of the benzyl group might govern diastereoselectivity in the addition step.

Although pharma researchers now routinely and reliably separate enantiomers by preparative chiral HPLC (24,25), an asymmetric variant of the present reaction sequence could be contemplated through the use of chiral directing groups or asymmetric electrocyclization catalysts (26,27). Moreover, the addition of many other types of nucleophiles should be possible, and the 1,2-dihydropyridine intermediates **4** could conceivably react with electrophiles other than proton to enable the regio- and stereoselective synthesis of even more densely substituted products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References and Notes

1. Typing the name of these drug and drug candidates into PubChem (<http://pubchem.ncbi.nlm.nih.gov/>) provides the compound structure, bioactivity, full list of published studies, and information regarding ongoing clinical trials, applications, and usage: plavix (CID 60606), cialis (110635), and aricept (CID 5741).
2. Lovering F, Bikker J, Humblet C. *J. Med. Chem.* 2009; 52:6752. [PubMed: 19827778]
3. Walters WP, Green J, Weiss JR, Murcko MA. *J. Med. Chem.* 2011; 54:6405. [PubMed: 21755928]
4. Ritchie TJ, Macdonald SJF. *Drug Discovery Today.* 2009; 14:1011. [PubMed: 19729075]
5. Doyle MP, Goldberg KI. C–H-Functionalization (Special Issue), *Acc. Chem. Res.* 2012; 45:777–958.
6. Davies HML, Du Bois J, Yu J-Q. C–H Functionalisation in Organic Synthesis (Special Issue), *Chem. Soc. Rev.* 2011; 40:1845–2040.
7. Crabtree R. Selective Functionalization of C–H Bonds (Special Issue), *Chem. Rev.* 2010; 110:575–1211.
8. Yamaguchi J, Yamaguchi AD, Itami K. *Angew. Chem. Int. Ed.* 2012; 51:8690.
9. Davies HML, Manning JR. *Nature.* 2008; 451:417. [PubMed: 18216847]
10. Wasa M, Engle KM, Yu J-Q. *J. Am. Chem. Soc.* 2010; 132:3680. [PubMed: 20187642]
11. Guimond N, Gorelsky SI, Fagnou K. *J. Am. Chem. Soc.* 2011; 133:6449. [PubMed: 21452842]
12. Colby DA, Bergman RG, Ellman JA. *J. Am. Chem. Soc.* 2008; 130:3645. [PubMed: 18302381]
13. Tietze, LF.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis.* Weinheim, Germany: John Wiley & Sons; 2006.
14. Davies HM, Sorensen EM. Rapid Complexity Generation in Natural Product Total Synthesis (Special Issue), *Chem. Soc. Rev.* 2009; 38:2969–3275.
15. Grondal C, Jeanty M, Enders D. *Nat. Chem.* 2010; 2:167. [PubMed: 21124474]
16. Bull JA, Mousseau JJ, Pelletier G, Charette AB. *Chem. Rev.* 2012; 112:2642. [PubMed: 22352938]
17. Duttwyler S, Lu C, Rheingold AL, Bergman RG, Ellman JA. *J. Am. Chem. Soc.* 2012; 134:4064. [PubMed: 22356093]
18. Lyle RE, Nelson DA, Anderson PS. *Tetrahedron Lett.* 1962; 3:553.
19. Anderson PS, Lyle RE. *Tetrahedron Lett.* 1964; 5:153.
20. Evans, DA. *Asymmetric Synthesis*, Volume 3. New York, USA: Academic Press; 1984. p. 20-21. p. 65-68.
21. Frisch, MJ., et al., editors. *Gaussian 09*, Revision A.1. Wallingford CT: Gaussian, Inc.; 2009.
22. Hoffman RW. *Chem. Rev.* 1989; 89:1841.
23. Liu H-J, Shia K-S, Shang X, Zhu B-Y. *Tetrahedron.* 1999; 55:3803.
24. Ward TJ, Ward KD. *Anal. Chem.* 2010; 82:4712. [PubMed: 20496871]
25. Okamoto Y, Ikai T. *Chem. Soc. Rev.* 2008; 37:2593. [PubMed: 19020674]
26. Thompson S S, Coyne AG, Knipe PC, Smith MD. *Chem. Soc. Rev.* 2011; 40:4217. [PubMed: 21566810]
27. Müller S, List B. *Angew. Chem. Int. Ed.* 2009; 48:9975.
28. van der Ent A, Onderlinden AL. *Inorg. Synth.* 1973; 14:92.
29. Hamper BC, Kurtzweil ML, Beck JP. *J. Org. Chem.* 1992; 57:5680.
30. LaPlante SR, Fader LD, Fandrick KR, Fandrick DR, Hucke O, Kemper R, Miller SPF, Edwards PJ. *J. Med. Chem.* 2011; 54:7005. [PubMed: 21848318]

31. Guthrie DB, Geib SJ, Curran DP. J. Am. Chem. Soc. 2011; 133:115. [PubMed: 21142031]
32. Rios R, Jimeno C, Carroll PJ, Walsh PJ. J. Am. Chem. Soc. 2002; 124:10272. [PubMed: 12197717]
33. Sheldrick GM. Acta Cryst. 1990; A46:467.
34. Sheldrick GM. Acta Cryst. 2008; A64:112.
35. Müller P. Crystallography Reviews. 2009; 15:57.

Fig. 1.
(A) Drugs containing a multiply substituted piperidine core; (B) rhodium-catalyzed synthesis of dihydropyridine intermediates leading to piperidine derivatives.

Fig. 2.

Four possible iminium ions resulting from protonation of dihydropyridine 4a.

Fig. 3. X-ray crystal structures (displayed with 50% displacement ellipsoids) of iminium ions (A1) *cis*-**5a** and (A2) *trans*-**6a**; calculated structures of (B1) *cis*-**5a** and (B2) *trans*-**6a**. Numbers are bond lengths in Å; H atoms have been omitted except when attached to saturated ring atoms.

Table 1

Substrate scope for the synthesis of products **7** and **8**.

Conditions A: 1:2 [RhCl(cyclooctene)₂]/4-Me₂NC₆H₄-PEt₂ (1–2.5 mol %), PhMe; B: (PhO)₂PO₂H, THF; C: Na[(AcO)₃BH], THF or R–[M], THF or Et₂O; D: PhSO₃H, CH₂Cl₂; E: R–[M], THF or Et₂O; for experimental details, see the Supplementary Material.

[†] [Rh] step run in THF, and reaction carried out as a one-pot procedure;

Rh step run in THF, and reduction conducted using $\text{Li}[\text{t-Bu}_3\text{BH}]$;

ref. (17) .