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Highly Diastereoselective Synthesis of Tetrahydropyridines by a C–H Activation–Cyclization–Reduction Cascade

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Abstract

A versatile reaction cascade leading to highly substituted 1,2,3,6-tetrahydropyridines has been developed. It comprises rhodium(I)-catalyzed C–H activation–alkyne coupling followed by electrocyclization and subsequent acid/borohydride-promoted reduction. This one pot procedure affords the target compounds in up to 95% yields and with >95% diastereomeric purity.

C–H bond functionalization has proven to be a powerful strategy for the assembly of pharmaceutically relevant classes of nitrogen heterocycles from simple and readily available precursors.^{1,2} We and others have in particular capitalized upon this approach to prepare highly substituted pyridines from alkynes and α,β -unsaturated imines, which in turn are derived from amines and diverse enones and enals (eq 1).³ Resonance stabilization of the heteroaromatic product provides a key driving force to enable this overall transformation to be accomplished by multiple mechanistically distinct pathways.

Herein, we utilize the same readily available starting materials to provide efficient access to highly substituted piperidine derivatives, a heterocycle class that is prevalent in a large number of bioactive natural products and drugs.^{4,5} Specifically, we report on a one pot cascade process to prepare tetrahydropyridines substituted at multiple sites in good yields and with very high diastereoselectivities (eq 2). This sequence enables the preparation of fully differentiated hexasubstituted piperidine derivatives, a level of differential substitution that to our knowledge has not previously been reported.⁶

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

Previous work³

(1)

This work

(2)

Rh-catalyzed β -C–H bond activation of α,β -unsaturated imines **1** followed by addition across alkynes **2** gives azatriene intermediates **3** that undergo electrocyclization in situ to give 1,2-dihydropyridines **4**.^{3b–d} We envisioned that these 1,2-dihydropyridines **4** could serve as very useful intermediates in a sequence leading to highly substituted piperidine derivatives as long as selective functionalization of the double bonds could be accomplished with high stereoselectivity. One avenue for achieving this goal would be stereoselective protonation of the enamine double bond followed by stereoselective reduction of the resulting iminium intermediate **5** to provide 1,2,3,6-tetrahydropyridines **6** (Scheme 1). The reduction of *N*-alkyl 1,2-dihydropyridines to 1,2,3,6-tetrahydropyridines via iminium intermediates is documented to proceed in good yields.⁷ However, for the vast majority of examples no stereocenters are introduced, and we could not identify any examples where this reduction sequence results in the introduction of two new stereocenters.

We therefore first chose to investigate reduction conditions using dihydropyridine **4e** as a test substrate. Alkenylation of imine **1e** in toluene at 80 °C using 2.5 mol % of [Rh(coe)₂Cl]₂ and 5 mol % of the 4-Me₂N-C₆H₄-PEt₂ ligand followed by in situ electrocyclization proceeded cleanly within 2 h to give **4e** in >90% NMR yield. Dihydropyridine **4e** was then subjected to a variety of reduction conditions (Table 1). At the outset, the toluene solution of **4e** was added to a suspension of NaBH₄ in ethanol at 0 °C, a procedure based upon previously reported conditions for reducing 1,2-dihydropyridines unsubstituted at the 5- and 6-positions. Unfortunately, only partial reduction to a mixture of tetrahydropyridines along with unidentified byproducts was observed (Table 1, entry 1).⁷ However, when the toluene solution of **4e** and an excess of acetic acid were added to the NaBH₄ suspension, GC-MS analysis indicated a much cleaner conversion to a mixture of four products, the major component of which was identified as **6e** (*vide infra*). Apparently, regio- and stereoselective protonation–reduction was considerably facilitated by a Brønsted acid.

Optimization of the reduction conditions indicated that both the nature of the acid and the reducing agent had an influence on the product distribution, but no significant counterion effect was observed (entries 3, 4, and 5). In addition, we suspected that the actual reducing species in entry 2 was (AcO)₃BH[–].⁸ Indeed, the use of (AcO)₃BH[–]/AcOH afforded **6e** in

high yield and diastereoselectivity; stronger acids lead to markedly worse results (entries 6–10). Based on these findings, the conditions listed in entry 6 were chosen for reductions involving other dihydropyridines.

A diverse set of imines **1** and alkynes **2** were next evaluated to test the scope of the cascade reaction (Table 2). The imines were obtained by condensation of the corresponding α,β -unsaturated ketone and a primary amine, the enones being commercially available or readily accessible by an aldol condensation.⁹ Upon completion of the alkenylation and cyclization steps, crude solutions of the dihydropyridines and acetic acid were added to a suspension of $\text{Na}(\text{AcO})_3\text{BH}$ in ethanol at 0 °C, and the resulting reaction mixtures were stirred at 0 °C to ambient temperature overnight.

Under the optimized reaction conditions, less substituted imines **1a–c** afforded tetrahydropyridines **6a–c** in excellent overall yields. For **6c**, where a single additional stereocenter was introduced, good diastereoselectivity was also observed. Most importantly, all hexasubstituted products showed outstanding diastereoselectivities with only a single diastereomer detectable by ¹H and ¹³C NMR spectroscopy except for the hindered *tert*-butyl substituted product **6j** and bicyclic product **6l**, for which a 10:5:3 and a 10:1:1 ratio of stereoisomers were observed, respectively.^{10a}

A variety of *N*-substituents were well tolerated, including *N*-benzyl (**6a–e,h–q**), branched *N*-alkyl (**6f**), and *N*-phenyl (**6g**) derivatives. Although 3-hexyne was employed as the alkyne input for the majority of examples, diphenylacetylene also provided the tetrahydropyridine **6h** in high yield and with excellent stereoselectivity. The unsymmetrical alkyne, isopropyl methyl acetylene, **2c**, afforded a 2:1 regioisomeric mixture of products that could be separated by silica gel chromatography.^{10b} In contrast, *t*-butyl methyl acetylene, **2d**, gave a single regioisomer upon C–H activation–cyclization; however, a mixture of diastereomers was obtained after reduction (vide infra). Notably, unsymmetrical alkyne **2e** bearing an ester functionality afforded **6k** as a single regio- and diastereoisomer.^{10c} A number of 4-phenyl and 4-heteroaryl tetrahydropyridines have been recognized as pharmacologically potent compounds.^{2,11} For this reason, we prepared imines **1i–l** containing furyl, pyrrolyl, and indolyl moieties, respectively, in addition to the phenyl-substituted derivatives **1b–d**. The corresponding tetrahydropyridine products were isolated in 52–95% yield (**6b–d** and **6m–q**). For **6p** no over-reduction of the indole ring system was observed.¹² Combination of imine **1e** with alkyne **2e** served to highlight the potential of the cascade process for introducing a maximum number of different piperidine substituents in a concise sequence. To the best of our knowledge, **6q** is the first example of a hexasubstituted, fully differentiated piperidine derivative.

The relative configuration of the saturated ring carbon atoms was established by X-ray crystallography: the structure of **6h** was solved as the free amine and **6e** and **6g** as the corresponding ammonium salts, unambiguously revealing all-*cis* stereochemistry.¹³ Based on these results and the similarities of the NMR spectra of all tetrahydropyridines, in addition to assuming similar reduction pathways, we assigned the all-*cis* configuration to the other products by analogy.

We rationalize the observed stereochemical outcome by a kinetically controlled protonation followed by face-selective borohydride reduction (shown for product **6e** in Scheme 2). The transition state **7e** leading from dihydropyridine **4e** to iminium ion **5e** exhibits N–C(2) double bond character.¹⁴ Due to allylic strain between the *N*-benzyl and C(5)-ethyl substituents, the conformation with Et–C(5) in a pseudoaxial position is preferred. Approach of the acid and proton transfer then occur in an *anti* fashion, affording *cis*-iminium ion **5e**.

This species is eventually reduced by $(\text{AcO})_3\text{BH}^-$, which delivers its hydride from the less hindered side to give all-*cis* product **6e**.

Additionally, we sought to extend the synthetic utility of the cascade sequence by providing an initial demonstration that nucleophiles other than hydride can be added to protonated dihydropyridines with high selectivity. Specifically, when isolated **4e** was treated stepwise with 2-naphthylsulfonic acid and allylcerium chloride, heptasubstituted piperidine derivative **8** was obtained in good yield as a single diastereomer (eq 3).^{15,16} The relative configuration of **8** was established by X-ray crystallography and points to a mechanism similar to that operative in the reactions leading to tetrahydropyridines **6**.

In conclusion, we have developed a cascade transformation that enables the one pot preparation of highly substituted piperidine derivatives **6** starting from imines and alkynes in good overall yields and with uniformly excellent diastereoselectivities. The broad scope and versatility of the cascade process was demonstrated by the introduction of a variety of alkyl, aryl and heteroaryl substituents at multiple sites in the tetrahydropyridine products.

(3)

The synthetic potential of dihydropyridine intermediates **4** was further accentuated by the demonstration that not only hydride but also carbon nucleophiles can be added with high diastereoselectivity to give heptasubstituted piperidine derivative **8**. Further expansion of this sequence to a broader set of carbon nucleophiles is actively being pursued as is the application of this cascade transformation to the rapid preparation of bioactive compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Reaction Cascade for the One Pot, Stereoselective Synthesis of Piperidine Derivatives.

Scheme 2.
Proposed Mechanism for the Stereoselective Reduction and Ball-and-Stick Representation
of **[6e-H]⁺**.¹³

Table 1Influence of Reduction Conditions on Yield and *dr* of Tetrahydropyridine 6e.^a

Entry	Reducing agent	Solvent/acid ^b	yield (%) ^c	<i>d.r.</i> ^c
1	NaBH ₄	PhMe–EtOH/–	(77) ^d	(54:46) ^d
2	NaBH ₄	PhMe–EtOH/AcOH	86	94:6
3	NaBH ₄	PhMe–EtOH/pivOH	84	65:35
4	Bu ₄ NBH ₄	PhMe–EtOH/AcOH	85	92:8
5	Na(CN)BH ₃	PhMe–EtOH/AcOH	87	68:32
6	Na(AcO)₃BH	PhMe–EtOH/AcOH	85	95:5
7	Me ₄ N(AcO) ₃ BH	PhMe–EtOH/AcOH	78	96:4
8	Me ₄ N(AcO) ₃ BH	PhMe–DCM/AcOH	81	89:11
9	Na(AcO) ₃ BH	PhMe–EtOH/TsOH	(35) ^d	(54:46) ^d
10	Na(AcO) ₃ BH	PhMe–EtOH/TFA	17	(27:73)

^a Reduction conditions: 20 μmol of dihydropyridine, 5 equiv of acid, 3 equiv of reducing agent, 0 °C for 2 h, then 0 °C to RT overnight.^b PhMe from Rh-mediated reaction, PhMe:EtOH or CH₂Cl₂ = 1:1; pivOH = pivalic acid, TsOH = *p*-toluenesulfonic acid; TFA = trifluoroacetic acid.^c Determined by GC-MS using 2,6-dimethoxytoluene as an internal standard; yield = total yield of tetrahydropyridine isomers with regard to imine starting material, *dr* = ratio of depicted all-*cis* product to sum of other diastereomers. The estimated error for GC integrals is ±3%.^d Approximate numbers; unidentified byproducts with overlapping retention times also formed.

Table 2

Substrate Scope of the Cascade Transformation.^a

Imine R ¹ -R ⁴	Alkyne R ⁵ -R ⁶	Pdt	Imine	Alkyne	Pdt		
1a Bn H H Me	2a Et Et	6a	1h	2a	6l		
1b Bn H H Ph	2a	6b					
1c Bn Me H Ph	2a	6c	1i	2a	6m		
1d Bn Me Me Ph	2a	6d					
1e Bn Me Me Me	2a	6e	1j	2a	6n		
1f Cy Me Me Me	2a	6f					
1g Ph Me Me Me	2a	6g	1k	2a	6o		
1e	2b Ph Ph	6h					
1e	2c <i>i</i> -Pr Me	6i	1l	2a	6p		
1e	2d <i>i</i> -Bu Me	6j					
1e	2e <i>i</i> -Pr CO ₂ Me	6k	1j	2e	6q

^aYields correspond to the overall yield of analytically pure product after silica gel chromatography and are based upon the α,β -unsaturated imine starting material. The diastereoselectivity was determined by ¹H NMR analysis of clearly resolved piperidine hydrogens. For full experimental details, see the Supporting Information.

^bAlkyne regioselectivity 2:1, combined yield for separated regioisomers.

^cCombined yield for regioisomerically pure, diastereomeric mixture.