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Skeletal Diversity through Radical Cyclization of Tetrahydropyridine Scaffolds

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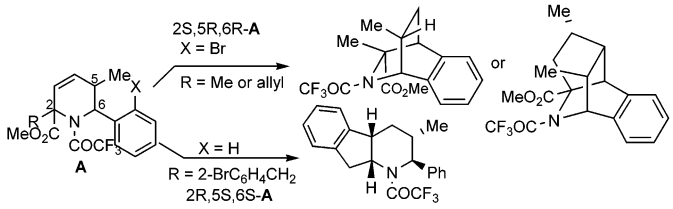
ABSTRACT



Suitably functionalized tetrahydropyridines (methyl pipecolates) have been used as conformationally biased templates for radical cyclizations to access benzoisoquinuclidines and linearly fused indenopiperidines. Variation of skeletal types is determined by location of a radical-initiating element.

Diversity generation by systematic variation of substituents around a given scaffold has remained central to library synthesis.[1] We reasoned that the emerging area of skeletal diversity[2] can potentially benefit by identifying suitable reactive intermediates that have broad yet predictable reactivity patterns in complex molecular frameworks. An underdeveloped approach to skeletal diversity involves design and synthesis of conformationally biased scaffolds for radical cyclizations. Generation, reactivity, and stereoselectivity of free radical intermediates have been well-studied,[3] and application of radical cyclization continues to attract attention in target-oriented synthesis.[3d,f,4] However, applications of radical chemistry to diversity-oriented synthesis[5] and generation of skeletal diversity remain underdeveloped. In this paper, we illustrate how the selection of reaction partners for [4 +2] annulation assembles pipecolate templates as radical cyclization precursors while strategically positioning radical-initiating sites at different locations. A stereroselective

(1) (a) Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997. (b) Tan, D. S.; Foley, M. A.; Shair, M. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 8565. (c) Pelish, H. E.; Westwood, N. J.; Feng, Y.; Kirchhausen, T.; Shair, M. D. *J. Am. Chem. Soc.* **2001**, *123*, 6740.

(2) (a) For a review on principles of skeletal diversity, see: Schreiber, S. L.; Burke, M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 46. (b) Micalizio, G. C.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 3272. (c) Micalizio, G. C.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 152. (d) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613. (e) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 14095. (f) Lei, X.; Zaarur, N.; Sherman, M. Y.; Porco, J. A. *J. Org. Chem.* **2005**, *70*, 6474. (g) Zacuto, M. J.; Leighton, J. L. *Org. Lett.* **2005**, *7*, 5525. (h) Arya, P.; Joseph, R.; Gan, Z.; Rakic, B. *Chem. Biol.* **2005**, *12*, 163. (i) Oguri, H.; Schreiber, S. L. *Org. Lett.* **2005**, *7*, 47. (j) Spiegel, D. A.; Schroeder, F. C.; Duvall, J. R. ; Schreiber S. L. *J. Am. Chem. Soc.* **2006**, *128*, 14766. (k) Chen, Y.; Porco, J. A. Panek, J. S. *Org. Lett.* **2007**, *9*, 1529.

(3) (a) Curran, D. P. *Synthesis* **1988**, *6*, 417. (b) Curran, D. P. *Synthesis* **1988**, *9*, 489. (c) *Radicals in Organic Synthesis, Volume 1: Basic Principles*, Renuad, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001. (d) *Radicals in Organic Synthesis, Volume 2: Applications*; Renuad, P., Sibi, M P., Eds.; Wiley-VCH: Weinheim, 2001. (e) Gansauer, A., Ed. Radicals in Synthesis I: Methods and Mechanisms. In *Top. Curr. Chem.* **2006**, *263*, 1−199. (f) Gansauer, A., Ed. Radicals in Synthesis II: Complex Molecules. In *Top. Curr. Chem.* **2006**, *264*, 1.

(4) (a) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134.

(5) (a) Ganesan, A.; Sibi, M. P. In *Handbook of Combinatorial Chemistry*; Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; Wiley-VCH: Weinheim, 2002; Vol. 1, p 227. (b) Gabarda, A. E.; Curran, D. P. *J. Comb. Chem.* **2003**, *5*, 617. (c) Tangirala, R.; Antony, S.; Agama, K.; Curran, D. P. *Synlett* **2005**, *18*, 2843.

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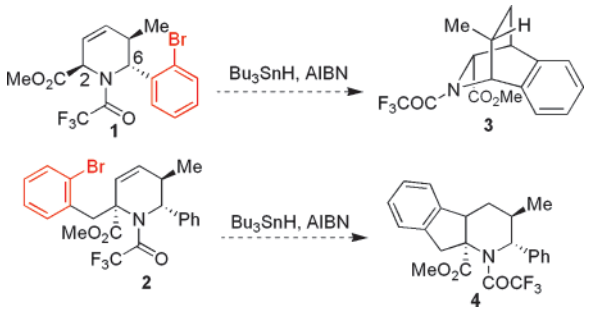
alkylation of the pipecolate scaffold is also used to install radical-initiating and -terminating sites.

We have previously reported stereoselective syntheses of both 2,6-cis- and 2,6-trans-substituted tetrahydropyridines employing intramolecular crotylation of imines derived from condensation of enantioenriched aminosilanes with aldehydes.[6] We anticipated that placement of a radical initiating site at different positions of a tetrahydropyridine scaffold **1** may enable different modes of radical additions to the C3−C4 double bond to generate novel alkaloidal structures (Scheme 1).[7] For example, in substrate **1** the 2-bromophenyl radical initiator element is placed at C6 while **3** has the 2-bromophenyl unit appended through the C2 position.

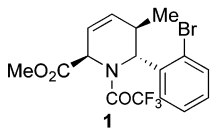
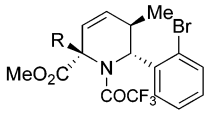
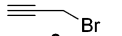
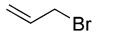
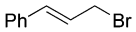
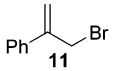
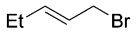
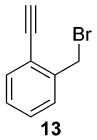
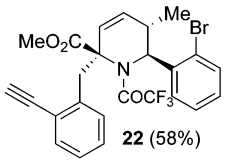
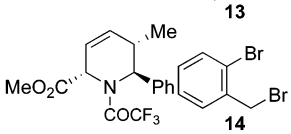
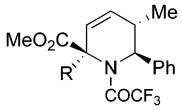
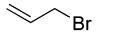
Scheme 1. Skeletal Diversity from Tetrahydropyridine Scaffolds



Different radical cyclization pathways of substrates **1** and **2** should thus generate complementary cyclized products **3** and **4**, respectively. It is also noteworthy that the new scaffolds are produced by a common mode of reaction (i.e., radical cyclization), so that there is no need to modify the reacting subunits (2-bromophenyl and the C−C double bond) to access different skeletal frameworks.

Preparation of radical cyclization substrates was carried out by alkylation of the dienolates species derived from tetrahydropyridine **1**. Treatment of **1** with LiHMDS and further reaction of the resulting dienolate with an alkyl halide provided the α-alkylation products with high diastereoselectivity.[8] Results of alkylation experiments are summarized in Table 1. For example, alkylation of **1** with methyl iodide resulted in the regio- and diastereoselective alkylation to afford product **15** in 85% isolated yield. In a similar manner, the *o*-bromophenyl-substituted tetrahydropyridine **1** was alkylated with propargyl, 3-methylpropargyl, allyl, and a range of substituted allyl halides (entries 2−7) in moderate to high yields. A 2-alkynylbenzyl group was also installed at the C2 position of ***ent*-1** using this alkylation procedure (entry 8). Tetrahydropyridine **5** bearing a phenyl group at

Table 1. Alkylation of Tetrahydropyridines[a,b]

entry	substrate	RX	product (yield[c])
1	 **1**	MeI **6**	 R = Me **15** (85%)
2	**1**	 **7**	R = $MeCCCH_2$, **16** (74%)
3	**1**	 **8**	R = $HCCCH_2$, **17** (74%)
4	**1**	 **9**	R = CH_2=$CHCH_2$, **18** (83%)
5	**1**	 **10**	R = *trans*-PhCH=$CHCH_2$, **19** (66%)
6	**1**	 **11**	R = CH_2=$C(Ph)CH_2$, **20** (70%)
7	**1**	 **12**	R = *trans*-EtCH=$CHCH_2$, **21** (66%)
8	***ent*-1**	 **13**	 **22** (58%)
9	 **5**	**14**	 R = 2-Br-C_6H_4-CH_2, **23** (74%)
10	**5**	 **9**	R = CH_2=$CHCH_2$, **24** (81%)

[a] LiHMDS (2 equiv), RX (5 equiv), HMPA (5.0 equiv), THF, −78 to 0 °C, 5 h. [b] Product was isolated as a single diastereomer. [c] Reported yield after silica gel chromatography.

C6 was also efficiently alkylated with both 2-bromobenzyl and allyl bromides (entries 9 and 10), respectively. In all cases examined, a single diastereomer was obtained.

Stereochemical assignment of the newly formed quaternary center was carried out using NOE measurements of product **15** which indicated that the two methyl groups are cis to each other.[8] The calculated ground-state structure of **15** and the observed NOE data are depicted in Figure 1A.[9] We rationalize the observed selectivity based on the calculated[9] structure of a lithium enolate derived from **1** wherein the electrophile approaches the enolate in a pseudoequatorial orientation (Figure 1B). As is evident from the model, axial approach of the electrophile would encounter severe steric interactions with the C6 aryl group.

A number of precursors were prepared with the 2-bromophenyl subunit at two different locations on the tetrahydropyridine core. We then investigated the feasibility of radical cyclizations to assemble novel frameworks such as

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(7) (a) Gan, Z.; Reddy, P. T.; Quevillon, S.; Couve-Bonnaire, S.; Arya, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 1366. (b) Reddy, P. T.; Quevillon, S.; Gan, Z.; Forbes, N.; Leek, D. M.; Arya, P. *J. Comb. Chem.* **2006**, *8*, 856.

(8) See the Supporting Information for complete experimental details.

(9) Conformational analysis was carried out using a Molecular Operating Environment (MOE) (version 2006.08) stochastic search.

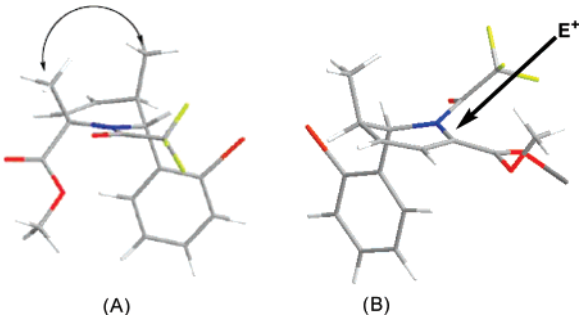
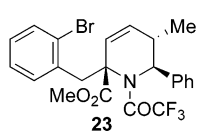
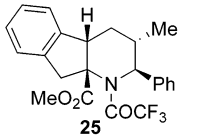
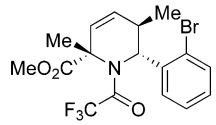
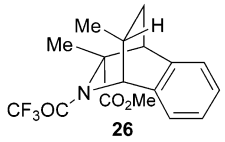
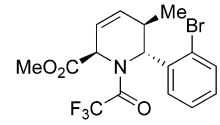
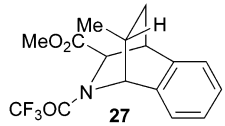
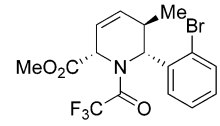
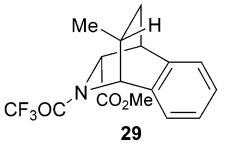


Figure 1. (A) Calculated ground-state structure of **15** with observed NOE indicated with arrow. (B) Proposed transition-state model for the stereochemical outcome of alkylation.

benzoisoquinuclidines and indenopiperidines. Treatment of **23** with tributyltin hydride in the presence of a catalytic amount of AIBN (80 °C) cleanly afforded the indenopiperidine **25** in 81% isolated yield (Table 2, entry 1). When

Table 2. Results of Radical Cyclizations with a Single C−C Bond Formation

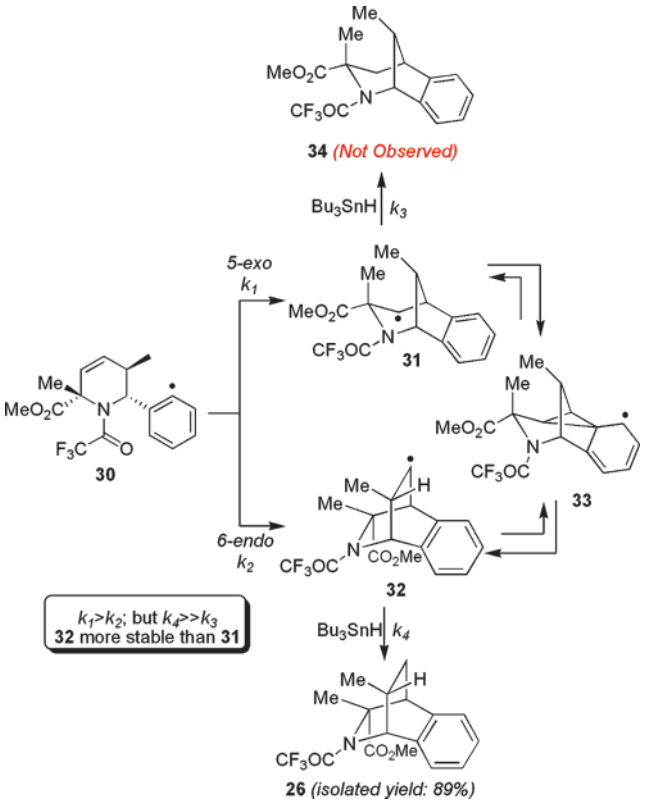
entry	substrate	product	yield
1[a]	 **23**	 **25**	81%
2[a]	 **21**	 **26**	89%
3[b]	 **1**	 **27**	71%
4[b]	 **28**	 **29**	77%

[a] AIBN, Bu_3SnH, 80 °C, 4 h, benzene. [b] AIBN, $(Me_3Si)_3SiH$ 80 °C, 4 h, benzene.

the methylated tetrahydropyridine **21** was subjected to these reaction conditions, benzoisoquinuclidine **26** was isolated as a single product in 89% yield (entry 2), illustrating the consequence of positional variation of the radical initiating site. Tetrahydropyridine **1** when subjected to radical cyclization with tributyltin hydride, afforded the benzoisoquinuclidine **27** with a small amount of an unidentified byproduct. After screening several different initiators and reducing agents, we found that **1** could be cleanly converted to **27** in 71% yield with the use of tris(trimethylsilyl)silane[10] and AIBN (entry 3). Under these modified conditions **28**, the C2 epimer of **1**, also gave the corresponding benzoisoquinuclidine **29** in 77% isolated yield (entry 4).

A mechanistic analysis and proposal for the high levels of regioselectivity leading to the formation of benzoisoquinuclidines is provided in Scheme 2. Aryl radical **30** can

Scheme 2. Mechanistic Analysis for Regioselectivity in Radical Cyclization of **21**



potentially partition via 5-*exo-trig* and 6-*endo-trig* pathways to intermediates **31** and **32**, respectively (Scheme 2). According to literature precedent,[3,11] radical intermediate **31** should be formed in greater amounts as 5-*exo-trig* cyclization is kinetically favored over the 6-*endo-trig* process. However, radicals **31** and **32** may equilibrate through the cyclopropylcarbinyl radical **33** by a neophyl rearrangement[12] ultimately favoring the more stable [2.2.2]bicyclo radical **32**. In addition, the rate of reduction of **31** by tributyltin hydride will also be significantly lower compared to that of **32** due

(10) Kanabus-Kaminska, J. M.; Hawari, J. A.; Griller, D.; Chatgilialoglu, C. *J. Am. Chem. Soc.* **1987**, *109*, 5267.

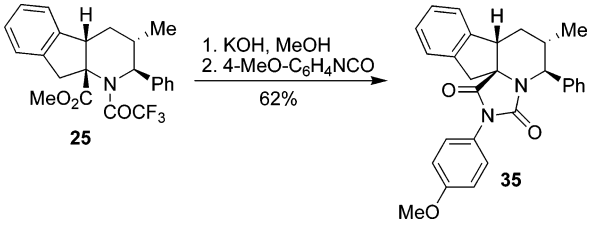
(11) Baldwin, J. E.; Lusch, M. J. *Tetrahedron* **1982**, *38*, 2939 (a) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140. (b) Yadav, V.; Fallis, A. G. *Tetrahedron Lett.* **1989**, *30*, 3283.

(12) (a) Beckwith, L, J.; O'Shea, D. M. *Tetrahedron Lett.* **1986**, *27*, 4525. (b) Stork, G.; Mook, R., Jr. *Tetrahedron Lett.* **1986**, *27*, 4529. (c) Ishibashi, H.; Kobayashi, T.; Nakashima, S.; Tamura, O. *J. Org. Chem.* **2000**, *65*, 9022. (d) Toyota, M.; Yokota, M.; Ihara, M. *J. Am. Chem. Soc.* **2001**, *123*, 1856.

to steric hindrance of the radical center in **31** by the adjacent quaternary center.[13]

To extend the utility of these scaffolds to access additional structural frameworks, indenopiperidine **25** was deacylated using methanolic KOH. The resulting amino acid was converted to the tetracyclic hydantoin **35** in 62% isolated yield over the two steps (Scheme 3).

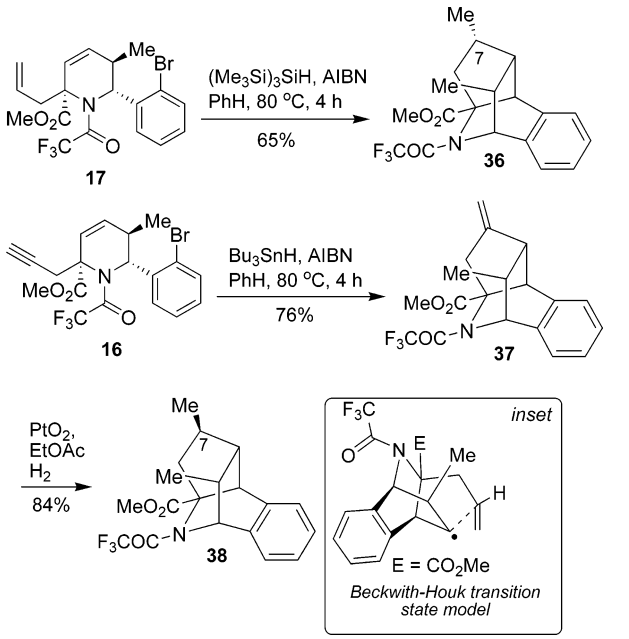
Scheme 3. Deprotection and Complex Hydantoin Formation



The high "6-*endo*-*trig*" selectivity observed for cyclization of **21** suggested that the intermediate radical formed in these reactions may be subjected to a second cyclization if a suitable radical acceptor is located at the C2 position of the tetrahydropyridine. Accordingly, treatment of the allylated tetrahydropyridine **17** with tris(trimethylsilyl)silane and AIBN in benzene at 80 °C resulted in tandem cyclization to produce scaffold **36** as a single diastereomer at C7 in 65% isolated yield (Scheme 4). The stereochemical outcome of this reaction may be rationalized by the Beckwith−Houk transition-state model[14] (inset, Scheme 4) where the exocyclic olefin is oriented away from the existing methyl group. We also designed a two-step sequence to access the C7 epimer of **36**. Tandem radical cyclization of the propargylated tetrahydropyridine **16** gave **37** in 76% yield, which was followed by hydrogenation of the exocyclic double bond using Adam's catalyst, which cleanly afforded the complex scaffold **38** as a single diastereomer bearing an epimeric relationship to **36** at C7.

In summary, radical cyclizations of tetrahydropyridine scaffolds have been used to access diverse skeletal frameworks. Stereoselective alkylations were employed to introduce both radical initiation and termination sites to the scaffolds for subsequent cyclizations. Indenopiperidines and benzoisoquinuclidines were readily accessed by radical cyclizations that form a single C−C bond. Complex benzoisoquinuclidines were also accessed by tandem radical cyclizations with attendant formation of two C−C bonds. Further studies, including library expansion and biological evaluation of the novel chemotypes, are currently under investigation and will be reported in due course.

Scheme 4. Tandem Radical Cyclizations with Two C−C Bond Formations



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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701722Z

(13) For a similar analysis of differences in rates of reduction based on steric encumbrance around the radical center, see ref 12c.

(14) (a) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. (b) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. (c) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959. (d) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996.