J|A|C|S COMMUNICATIONS

Published on Web 02/22/2010

Enantioselective Synthesis of Angularly Substituted 1-Azabicyclic Ring Systems: Dynamic Kinetic Resolution Using Aza-Cope Rearrangements

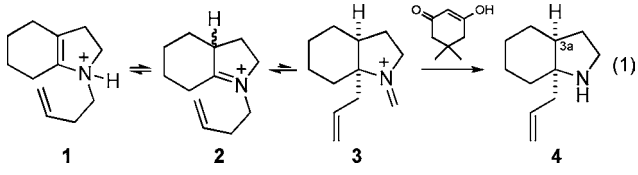
Tatsuya Ito,† Larry E. Overman,* and Jocelyn Wang

Department of Chemistry, University of California, Irvine, 1102 Natural Sciences II, Irvine, California 92697-2025

Received January 22, 2010; E-mail: leoverma@uci.edu

1-Azabicyclic ring systems having angular substituents adjacent to nitrogen are structural motifs found in a variety of alkaloid natural products and biologically active agents.[1] Despite the presence of these moieties in compounds of interest, few general methods for their enantioselective synthesis have been reported.[2] In this report, we describe a general enantioselective synthesis of such 1-azabicyclic frameworks that introduces a new strategy for achieving dynamic kinetic resolution in the formation of C−C bonds.

Previously, we described the construction of racemic 1-azabicyclic products such as octahydroindole **4** by a novel sequence in which the less stable isomer **3** of a cationic 2-aza-Cope equilibration is trapped by dimedone (eq 1).[3] During investigations of the reaction mechanism, we observed that deuterium was incorporated from MeOD into the angular 3a position of product **4**, signifying that the starting iminium cation **2** rapidly equilibrated with enamonium isomer **1**. Such a rapid pre-equilibrium suggested that introduction of a nonracemic stereocenter into the homoallylic side chain of precursor **2** might result in a dynamic kinetic resolution to deliver largely one enantiomer of the 1-azabicyclic product.[4]



The proposed dynamic kinetic resolution was first explored with substrates having a substituent at the homoallylic carbon of the side chain of the starting iminium ion **2**.[4] A phenyl substituent provided the highest degree of chirality transfer, although the chirality transfer was not complete. However, complete transfer of chirality from a nonracemic side chain was realized when a phenyl substituent was incorporated at the allylic carbon.[5]

The optimized sequence that was developed is summarized for the synthesis of octahydrocyclopenta[*b*]pyrrole **8** in Scheme 1. The carboxylic acid derived from ketal ester **5**, which is available in two steps from cyclopentanone,[3,4] was coupled with enantioenriched amine **6**, and the resulting amide was reduced with lithium aluminum hydride to give secondary homoallylic amine **7** in 61% yield over three steps.[6] (*R*)-2-Phenyl-3-butenamine (**6**, 99% ee) is available on a multigram scale from molybdenum-catalyzed asymmetric allylic substitution of cinnamyl methyl carbonate with dimethyl sodiomalonate,[7] followed by conventional elaboration of the product to the primary amine.[6] Aminoketal **7** was heated at 120 °C for 30 min with 1 equiv of CF_3CO_2H (TFA), 2.5 equiv of dimedone, and 0.1 equiv of morpholine in the absence of solvent to provide azabicyclic amine **8**, which was converted to its Cbz derivative to facilitate purification and analysis.

Scheme 1. Enantioselective Synthesis of 1-Azabicyclo[3.3.0]octane **8**

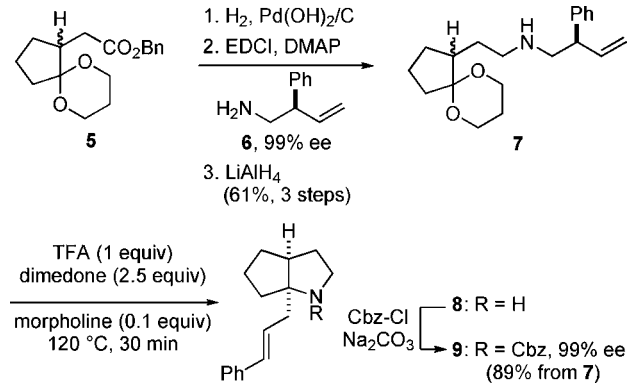
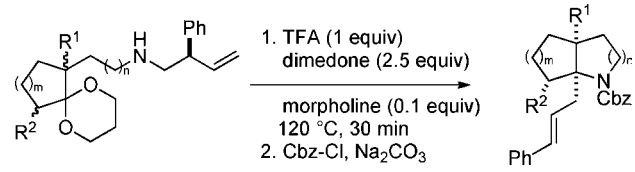


Table 1. Enantioselective Synthesis of Substituted 1-Azabicyclics



entry	*m*	*n*	R^1	R^2	product	yield (%)	ee (%)[a]
1	1	1	H	H	**9**	89	99
2	2	1	H	H	**10**	82	99
3	3	1	H	H	**11**	79	99
4	1	2	H	H	**12**[b]	89	99
5	2	2	H	H	**13**[b]	86[c]	99[d]
6	2	1	H	Me	**14**[b]	81	99
7[e]	2	1	Me	H	**15**[b]	48	99

[a] Enantiomeric excess was determined using enantioselective HPLC. [b] Relative configuration was determined from NOESY data. [c] A 1.7:1 mixture of cis and trans stereoisomers. [d] For both diastereomers. [e] Time was 1 h.

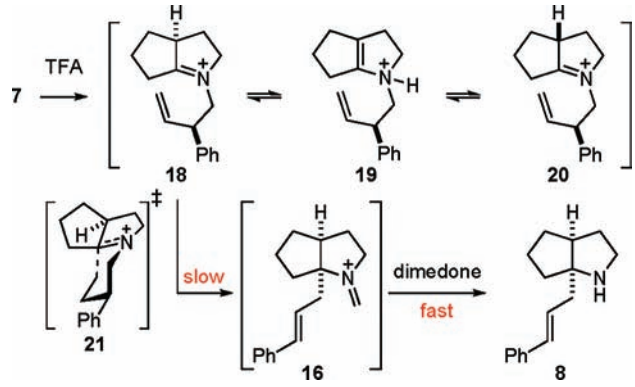
In this way, azabicyclic carbamate **9** was obtained in 89% yield and 99% ee, indicating complete transfer of chirality from the allylic stereocenter. To emphasize the synthetic utility of the reaction, the transformation of aminoketal **7** was conducted on a 1 g scale to furnish heterocycle **9** in 99% ee and 87% yield.[8]

The scope of this enantioselective synthesis can be seen in the results summarized in Table 1. Angularly substituted octahydroindole **10**, decahydrocyclohepta[*b*]pyrrole **11**, and octahydrocyclopenta[*b*]pyridine **12** were all formed in good yields and 99% ee exclusively as the cis stereoisomers (entries 2−4). Diastereoselection was lower in the formation of decahydroquinoline **13** (cis/trans = 1.7:1), with the readily separable stereoisomers each generated in 99% ee (entry 5). Methyl-substituted *cis*-octahydroindole **14** was formed exclusively as the all-cis stereoisomer (81% yield and 99% ee) from a precursor that was a mixture of four diastereomers (entry 6); this result established that both carbons adjacent to the ketal in the starting carbocyclic ring can be

† Current address: Chemical Development Laboratories, Pharmaceutical Product Division, Takeda Pharmaceutical Company Limited, 2-17-85 Jusohonmachi, Yodogawa-ku, Osaka 532-8686, Japan.

10.1021/ja100607z

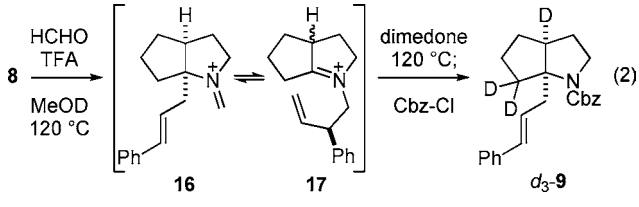
Scheme 2. Proposed Mechanism of Dynamic Kinetic Resolution



epimerized by iminium ion/enamonium equilibration.[3] The absolute configuration of 1-azabicyclic product **12** was established by single-crystal analysis of the corresponding secondary amine hydrobromide salt, and those of products **9** and **10** were obtained by chemical correlation;[6] absolute configurations of other products were assigned by analogy.

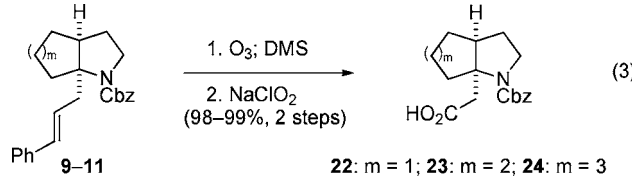
The success of the dynamic kinetic resolution to form 1-azabicyclic products **9**−**14** suggested that this strategy could be employed to kinetically resolve aminoketals containing an additional substituent R^1. This possibility was demonstrated by the formation of *cis*-octahydroindole **15**, in which both angular carbons are fully substituted, in 48% yield (Table 1, entry 7).

Our current understanding of this new approach to dynamic kinetic resolution derives from the following experiments. When the reaction of aminoketal **7** was carried out in deuterated methanol (1 equiv of TFA, 120 °C, sealed tube), azabicyclic product d_3-**9** was produced, as expected for rapid iminium ion/enamonium equilibration.[3] Product d_3-**9** was also formed when azabicyclooctane **8** was allowed to react with 3 equiv of paraformaldehyde (1 equiv of TFA, 120 °C, MeOD, sealed tube) in the absence of dimedone for 24 h, followed by addition of dimedone and conversion to the Cbz derivative; this result establishes that *in the absence of dimedone*, iminium ion isomers **16** and **17** equilibrate under the reaction conditions (eq 2). However, trapping with dimedone is irreversible, as the attempted reaction of secondary amine **8** with the formaldehyde/dimedone adduct[9] (1 equiv of TFA, 120 °C, MeOD, 20 h, sealed tube; CbzCl) provided azabicyclooctanyl carbamate **9** devoid of deuterium.



In light of these results, we propose the following mechanism (Scheme 2). Reaction of aminoketal **7** with TFA establishes a rapid pre-equilibration between iminium ion diastereomers **18** and **20** and enamonium ion **19**.[10] The cationic 2-aza-Cope rearrangement occurs more slowly and preferentially from iminium ion diastereomer **18** by favored chair transition structure **21**. Dimedone irreversibly traps the thermodynamically less stable iminium ion product **16**, giving 1-azabicyclic product **8** in high enantiomeric purity, more rapidly than formaldiminium ion **16** reverts to the equilibrium mixture of cations **18**, **19**, and **20**.[11]

To highlight some potential uses of this family of enantiopure amines, several products were converted in high yield to previously unknown β-amino acids, potentially valuable inputs for the synthesis of peptidomimetics and scaffolds for medicinal chemistry (eq 3).[12]



A useful enantioselective synthesis of angularly substituted 1-azabicyclic molecules that delivers the product amines in exceptionally high enantiopurity has been reported. This synthesis introduces a new strategy for dynamic kinetic resolution in which a rapid tautomeric equilibration of diastereomeric iminium cations is combined with a diastereoselective sigmatropic rearrangement. Experiments to further develop the scope of this method and obtain a deeper understanding of its mechanism are currently underway.

Acknowledgment. The NIH National Institute of Neurological Disorders and Stroke (NS-12389) and Takeda Pharmaceutical Co. supported this research. NMR and mass spectra and X-ray analyses were obtained at UC Irvine using instrumentation acquired with the assistance of NSF and NIH shared instrumentation programs. We thank Zach Aron (University of Indiana) for suggestions and early experiments.

Supporting Information Available: Experimental details, copies of ^{1}H and ^{13}C NMR spectra of new compounds and HPLC traces used to determine ee, a scheme showing all of the potential chair- and boat-topography aza-Cope rearrangements of **18** and **20**, and a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Aron, Z. D. Ph.D. Dissertation, University of California, Irvine, CA, 2004.
(5) Details of these experiments and optimization of the sequence reported in Scheme 1 will be discussed in a future full account of this work.
(6) Full experimental details are provided in the Supporting Information.
(7) (a) Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104. (b) Kaiser, N. K.; Bremberg, U.; Larhed, M.; Moberg, C.; Hallberg, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3596. (c) Palucki, M.; Um, J. M.; Conlon, D. A.; Yasuda, N.; Hughes, D. L.; Mao, B.; Wang, J.; Reider, P. J. *Adv. Synth. Catal.* **2001**, *343*, 46.
(8) Morpholine was not present in this reaction. In small-scale reactions, morpholine is added to insure that excess TFA is not present; dimedone decomposes at high temperature in the presence of TFA.
(9) 2,2′-Methylenebis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one).
(10) Exposure of aminoketal **7** to TFA at room temperature in $CDCl_3$ gave the tetrasubstituted iminium ion **18**/**20** and enamonium ion tautomers (^{1}H NMR analysis); formaldiminium ion **16** was not observed.
(11) (a) If formaldiminium ion **16** were in equilibrium with tetrasubstituted iminium ions **18** and **20** in the presence of dimedone, product **8** would be formed as a racemate because sigmatropic rearrangement of **20** across the convex face by a boat-geometry transition structure would lead to *ent*-**16**. (b) Rearrangement of **20** across the convex face by a chair transition structure would place the phenyl substituent in a quasi-axial orientation, giving the (*Z*)-styrenyl isomer of *ent*-**8**. Calibrated HPLC analysis of the crude reaction mixture indicated that **8** was produced as a 151:1 mixture of *E* and *Z* stereoisomers. (c) See the Supporting Information for a scheme showing all of the potential chair- and boat-topography aza-Cope rearrangements of intermediates **18** and **20**.
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JA100607Z