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

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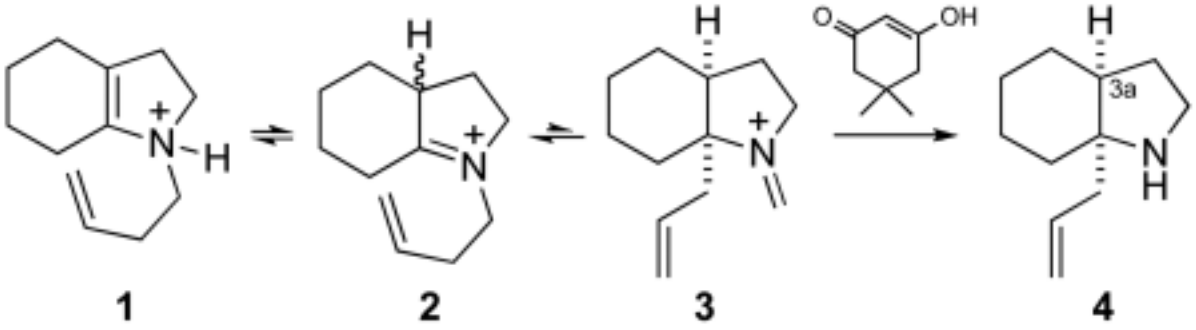
1-Azabicyclic ring systems having angular substituents adjacent to nitrogen are structural motifs found in a variety of alkaloid natural products and biologically active agents.[1] Despite the presence of these moieties in compounds of interest, few general methods have been reported for their enantioselective synthesis.[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 non-racemic 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]



(1)

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 chirality

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Supporting Information **Available**: Experimental details; copies of ^{1}H and ^{13}C NMR spectra of new compounds and of HPLC traces used to determine ee; a scheme showing all 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.

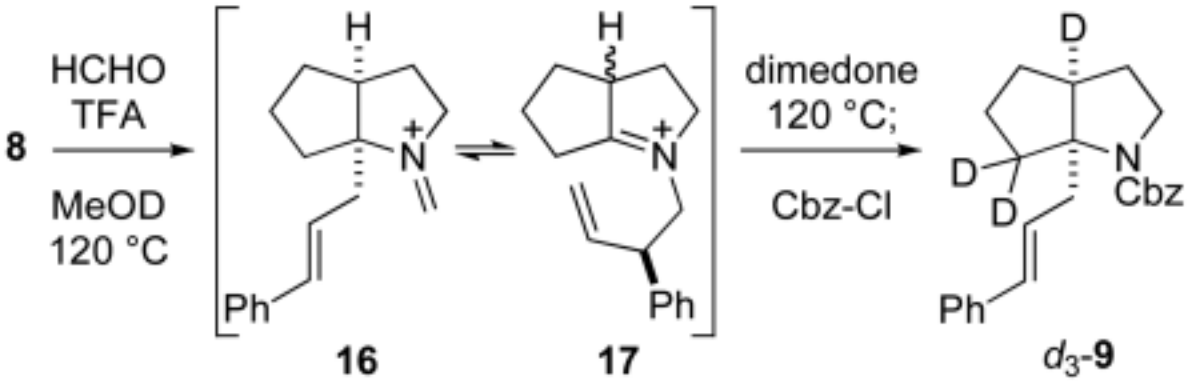
transfer was not complete. However, complete transfer of chirality from a non-racemic side chain was realized when a phenyl substituent was incorporated at the allylic carbon.[5]

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 3 steps.[6] (*R*)-2-Phenyl-3-butenamine (**6**, 99% ee) is available on 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. 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-gram scale to furnish heterocycle **8** 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, as exclusively 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 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 that of products **9** and **10** 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 in 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 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 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 attempted reaction of secondary amine **8** with the formaldehyde/dimedone adduct[9] (1 equiv TFA, 120 °C, MeOD, 20 h, sealed tube; CbzCl) provided azabicyclooctanyl carbamate **9** devoid of deuterium.



(2)

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** to give 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]

(3)

A useful enantioselective synthesis of angularly substituted 1-azabicyclic molecules is reported that delivers the product amines in exceptionally high enantiopurity. 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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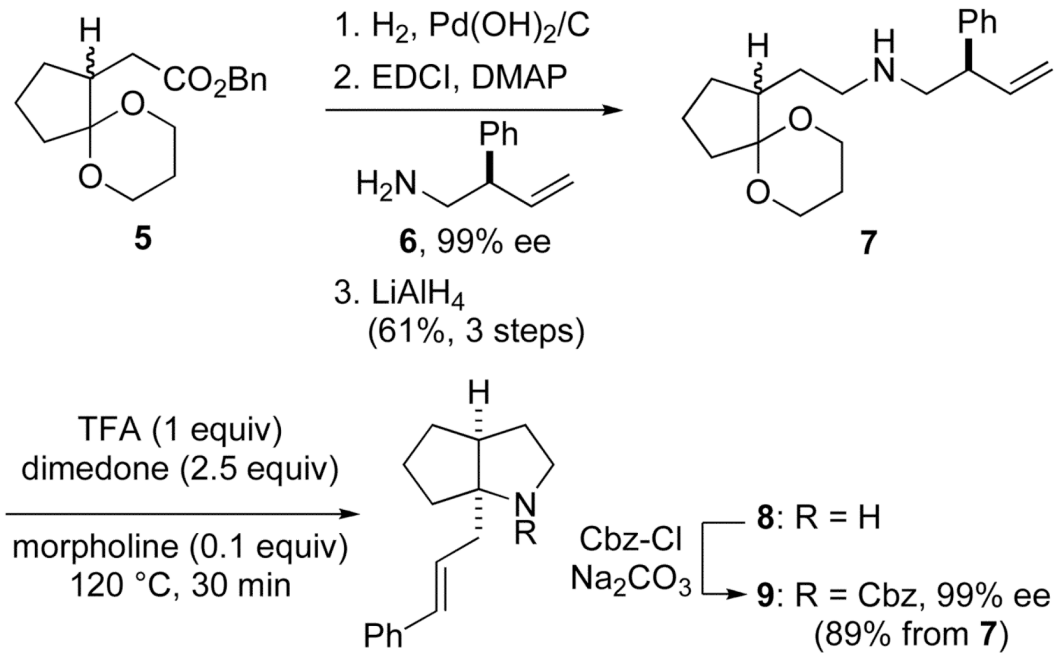
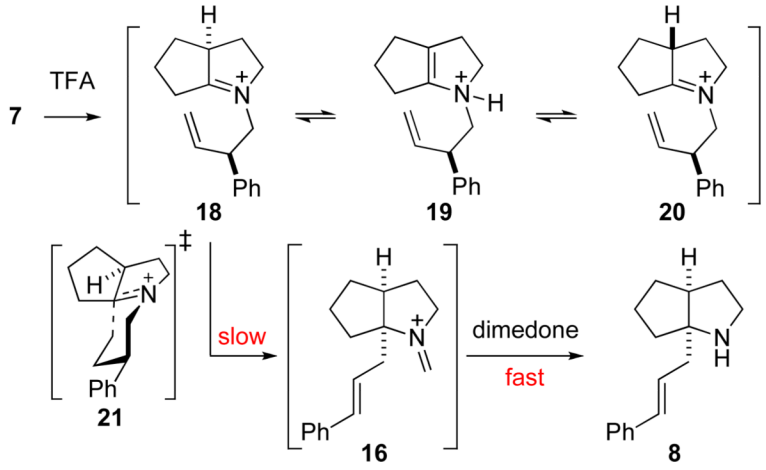
2. (a) Reggelin M, Junker B, Heinrich T, Slavik S, Bühle P. J Am Chem Soc 2006;128:4023–4034. [PubMed: 16551111] (b) Reggelin M, Slavik S, Bühle P. Org Lett 2008;10:4081–4084. [PubMed: 18712875]
3. Aron ZD, Overman LE. Org Lett 2005;7:913–916. [PubMed: 15727473]
4. Aron, ZD. PhD Dissertation. University of California; Irvine: 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 BM, Hachiya I. J Am Chem Soc 1998;120:1104–1105. (b) Kaiser NK, Bremberg U, Larhed M, Moberg C, Hallberg A. Angew Chem Int Ed 2000;39:3596–3598. (c) Palucki M, Um JM, Conlon DA, Yasuda N, Hughes DL, Mao B, Wang J, Reider PJ. Adv Synth Catal 2001;343:46–50.
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 trifluoroacetic acid at room temperature in $CDCl_3$, gives 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** was in equilibrium with tetrasubstituted iminium ions **18** and **20** when dimedone was present, product **8** would be formed as a racemate, because sigmatropic rearrangement of **20** across the convex face by a boat topography 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 indicates that **8** is produced as a 151:1 mixture of *E*:*Z* stereoisomers. (c) See Supporting Information for a scheme showing all potential chair and boat topography aza-Cope rearrangements of intermediates **18** and **20**.
12. (a) Seebach D, Gardiner J. Acc Chem Res 2008;41:1366–1375. [PubMed: 18578513] (b) Cheng RP, Gellman SH, DeGrado WF. Chem Rev 2001;101:3219–3232. [PubMed: 11710070]



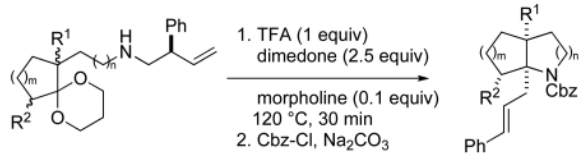
Scheme 1.
Enantioselective Synthesis of 1-Azabicyclo[3.3.0]octane **8**



Scheme 2.
Proposed Mechanism of Dynamic Kinetic Resolution

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 by enantioselective HPLC.

[b] Relative configuration was determined by NOESY data.

[c] A 1.7:1 mixture of *cis* and *trans* stereoisomers.

[d] For both diastereomers.

[e] Time was 1 h.

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