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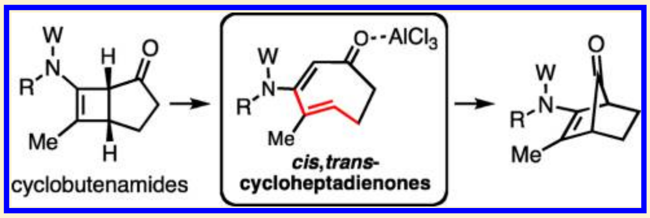
$AlCl_3$-Catalyzed Ring Expansion Cascades of Bicyclic Cyclobutenamides Involving Highly Strained *Cis,Trans*-Cycloheptadienone Intermediates

Xiao-Na Wang,[†,‡] Elizabeth H. Krenske,[*,§] Ryne C. Johnston,[§,¶] K. N. Houk,[*,∥] and Richard P. Hsung[*,‡]

[†]School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou, Henan 450001 P. R. China
[‡]Division of Pharmaceutical Sciences and Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53705 United States
[§]School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, Queensland 4072, Australia
[∥]Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095 United States

Supporting Information

ABSTRACT: We report the first experimental evidence for the generation of highly strained *cis,trans*-cycloheptadienones by electrocyclic ring opening of 4,5-fused cyclobutenamides. In the presence of $AlCl_3$, the cyclobutenamides rearrange to [2.2.1]-bicyclic ketones; DFT calculations provide evidence for a mechanism involving torquoselective 4π-electrocyclic ring opening to a *cis,trans*-cycloheptadienone followed by a Nazarov-like recyclization and a 1,2-alkyl shift. Similarly, 4,6-fused cyclobutenamides undergo $AlCl_3$-catalyzed rearrangements to [3.2.1]-bicyclic ketones through *cis,trans*-cyclooctadienone intermediates. The products can be further elaborated via facile cascade reactions to give complex tri- and tetracyclic molecules.

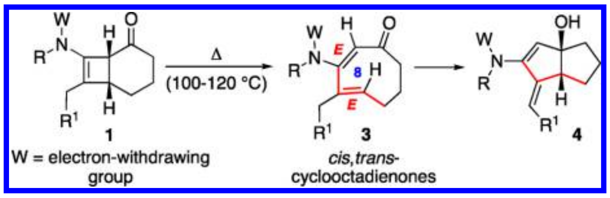


INTRODUCTION

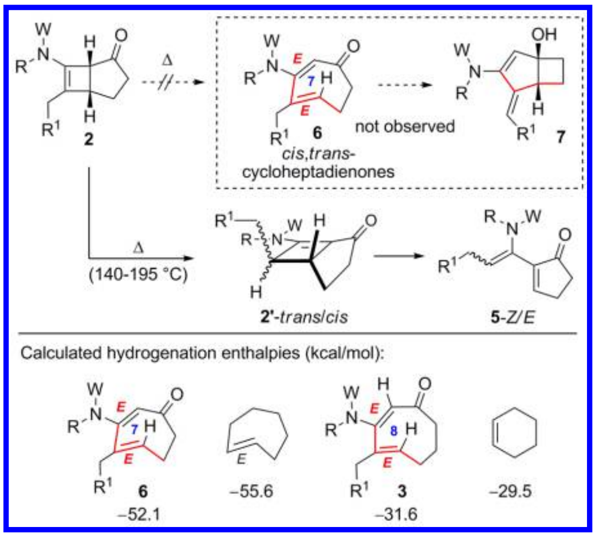
Small-ring *trans*-cycloalkenes have unique structural properties and reactivities, arising from the distortion of the double bond and the associated ring strain.[1−6] Among the parent *trans*-cycloalkenes, *trans*-cyclooctene is an isolable compound,[2f] while *trans*-cycloheptene has a lifetime of several minutes at −10 °C, and *trans*-cyclohexene is a fleeting intermediate formed by photolysis of the *cis* isomer.[2d] Strain-induced reactivity of *trans*-cycloalkenes has found applications in bioconjugate chemistry, where strain-promoted [4 + 2] cycloadditions of *trans*-cyclooctenes with tetrazines have been utilized for protein labeling and cellular imaging.[1d]

Recently, we reported[7] a new entry point into *trans*-cycloalkene chemistry involving rearrangements of readily prepared[8−11] cyclobutenamides **1** and **2** (Schemes 1 and 2). Under thermal conditions, 4,6-fused cyclobutenamides **1** rearrange to pentalenes **4** via *E,E*-cyclooctadienones **3**, which contain one *cis* and one *trans* double bond. Highly torquoselective ring opening of **1** to the *E,E*-isomer of **3**, followed by Nazarov-type recyclization, was supported by theoretical studies.

Scheme 1. Thermal Rearrangements of 4,6-Fused Cyclobutenamides 1



Scheme 2. Thermal Rearrangements of 4,5-Fused Cyclobutenamides 2



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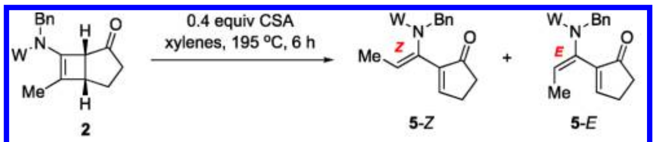
In contrast to **1**, thermal reactions of 4,5-fused cyclobutenamides **2** gave 2-amidodienes **5**. These products arise from isomerization of **2** to **2′** and do not involve formation of cycloheptadienones **6**.[10,11] Nevertheless, we sought suitable conditions to generate the highly strained cycloheptadienones, because theory predicted[7] that ring opening of **2** to **6** has a similar barrier to the opening of **1** to **3**. We now report evidence for the generation of these highly strained cycloheptadienone intermediates in $AlCl_3$-catalyzed rearrangements of **2**. The Lewis acid-catalyzed rearrangements yield different products from the corresponding thermal and Brønsted acid-catalyzed rearrangements and trigger cascade reactions leading to complex polycyclic molecules.

■ RESULTS AND DISCUSSION

We first examined the effects of Brønsted acid on the rearrangements of **2** (Figure 1). In the presence of 0.4 equiv



W	yield [%]^a	Z:E^b
2a: Ns	5a: 89	3.5:1
2b: Ts	5b: 92	5:1
2c: Mbs	5c: 88	5:1

Figure 1. Brønsted acid-catalyzed rearrangements of 4,5-fused cyclobutenamides **2** to 2-amidodienes **5** (*a*, isolated yields *b*, ratios determined by ^{1}H NMR spectroscopy).

camphorsulfonic acid (CSA), cyclobutenamides **2** rearranged to 2-amidodienes **5**, the same products as obtained from thermal rearrangements.[7,12−14] The Brønsted acid-mediated rearrangements were higher yielding and faster than the thermal reactions, presumably because the acid catalyzes the isomerization of **2** to **2′** (which is rate limiting under thermal conditions).[7] In contrast to **2**, 4,6-fused cyclobutenamides **1** containing the cyclohexanone instead of cyclopentanone (Scheme 1) were found to decompose in the presence of 0.4 equiv CSA.

Different reactivity was observed when rearrangements of **2** were conducted in the presence of a Lewis acid (Figure 2). Treatment of **2a** with 0.4 equiv $AlCl_3$ (toluene, 105 °C) gave [2.2.1]-bicyclic ketone **8a** in 68% yield. The structure of **8a** was unambiguously assigned via its single-crystal X-ray structure (Figure 2), and minor quantities of 2-amidodiene **5a** (10%) were also isolated, exclusively as the *Z* isomer.[15] Similar products were obtained from $AlCl_3$-catalyzed rearrangements of cyclobutenamides **2b** and **2c**, which bear Ts and Mbs groups, respectively, on nitrogen.

We considered two alternative mechanisms for the $AlCl_3$-catalyzed rearrangement of **2** to **8** (Scheme 3). In Path A, a sequence of two 1,2-alkyl shifts converts $AlCl_3$-coordinated cyclobutenamide **9** into [2.2.1]-bicyclic **12** via intermediate **11**. In Path B, the cyclobutenamide undergoes electrocyclic ring opening to coordinated cycloheptadienone **10**, followed by Nazarov-like recyclization to **11** and then a 1,2-alkyl shift giving **12**.

Density functional theory (DFT) calculations[16] provided insights into the rearrangement mechanism and the role of the Lewis acid. Figure 3 shows the computed free energy profiles

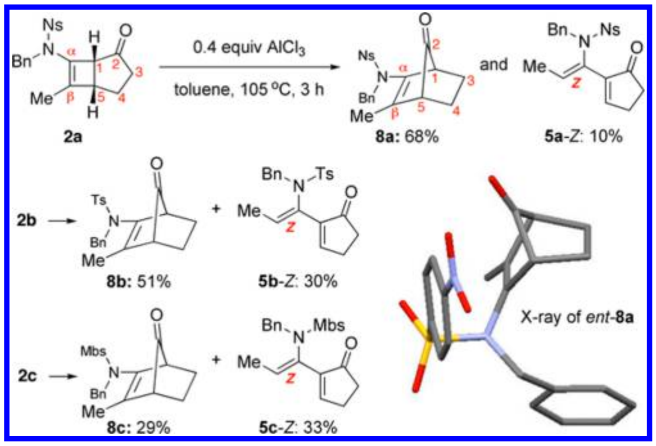
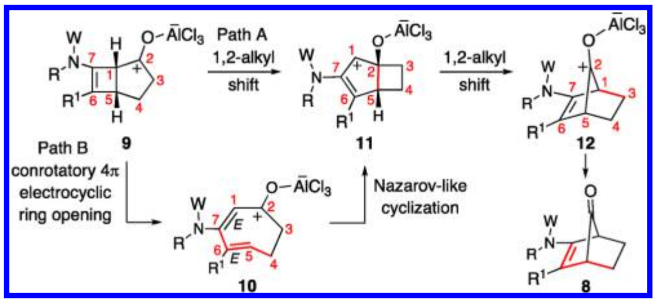


Figure 2. $AlCl_3$-catalyzed rearrangements of 4,5-fused cyclobutenamides **2** to [2.2.1]-bicyclic ketones **8** (*a*, isolated yields *b*, ratios determined by ^{1}H NMR spectroscopy).

Scheme 3. Two Possible Pathways for the $AlCl_3$-Catalyzed Rearrangement of Cyclobutenamides 2 to Ketones 8



for the thermal and $AlCl_3$-catalyzed rearrangements of **2** in toluene. Calculations were performed at the M06-2X/6-311+G(d,p)//B3LYP/6-31G(d) level of theory,[17,18] simulating the solvent with the SMD model.[19] All attempts to locate the first 1,2 shift transition state (TS) in Path A led instead to electrocyclic ring opening. The conformation required for a 1,2 shift TS, in which C-1 and C-2 must be coplanar, is effectively the same as that required for ring opening.[20] Moreover, ring opening is thermodynamically favored by the extended conjugation in pentenyl cation **10** as compared to allyl cation **11**.[21] The calculations therefore support Path B. Coordination of the cyclobutenamide to $AlCl_3$ significantly accelerates ring opening: the barrier for ring opening of **9** ($\Delta G^{\ddagger}$ = 28.3 kcal/mol) is 5 kcal/mol lower than that for opening of **2** (33.1 kcal/mol). The intermediate cycloheptadienone is stabilized by about 3 kcal/mol by coordination to $AlCl_3$ (**10** vs **6**). The torquoselectivity of ring opening, favoring the *E*,*E*- rather than the *Z*,*Z*-isomer of **10**, is predictable based on the established effects of donor and acceptor groups on cyclobutene ring opening.[22]

Nazarov-like cyclization of cycloheptadienone **10** furnishes **11**, which undergoes a 1,2-alkyl shift to give **12**. Both of these steps have barriers that are 4 kcal/mol lower than that for cyclobutenamide ring opening. The overall transformation of **9** to **12** is thermodynamically favored by 4 kcal/mol.[23] In contrast, uncatalyzed rearrangement of **2** may proceed only as far as **7**, which is uphill by 10.4 kcal/mol. Thus, coordination to $AlCl_3$ serves both to activate the cyclobutenamide toward cycloheptadienone formation and to provide a low-energy pathway for cycloheptadienone rearrangement that is not

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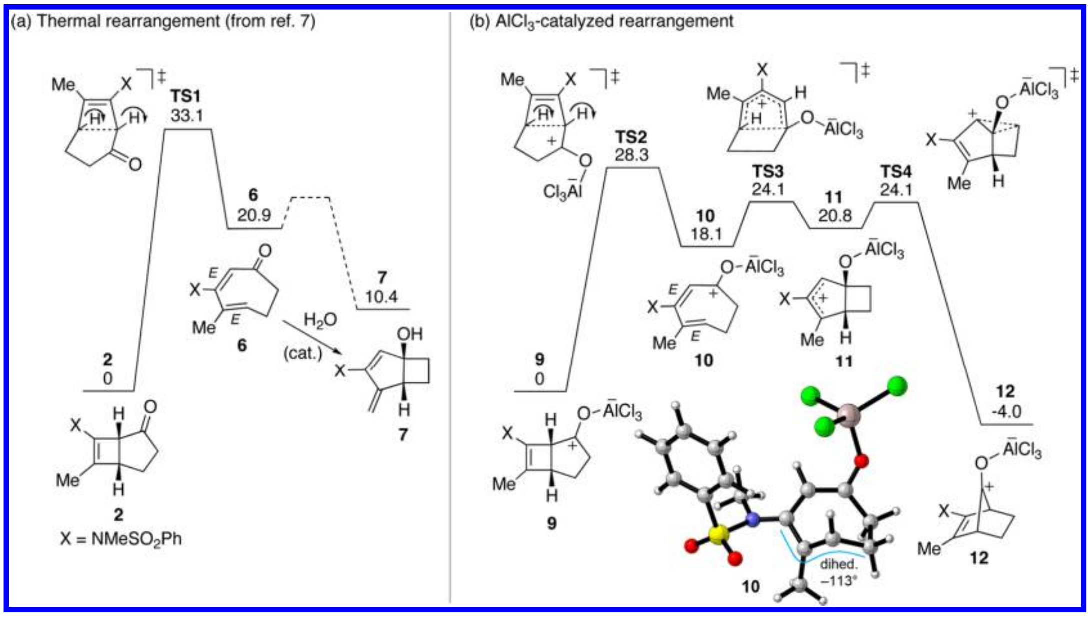

Figure 3. Free energy profiles for (a) thermal[7] and (b) $AlCl_3$-catalyzed rearrangements of 4,5-fused cyclobutenamide **2** in toluene, calculated at the M06-2X/6-311+G(d,p)//B3LYP/6-31G(d) level of theory with SMD solvent corrections. ΔG in kcal/mol.

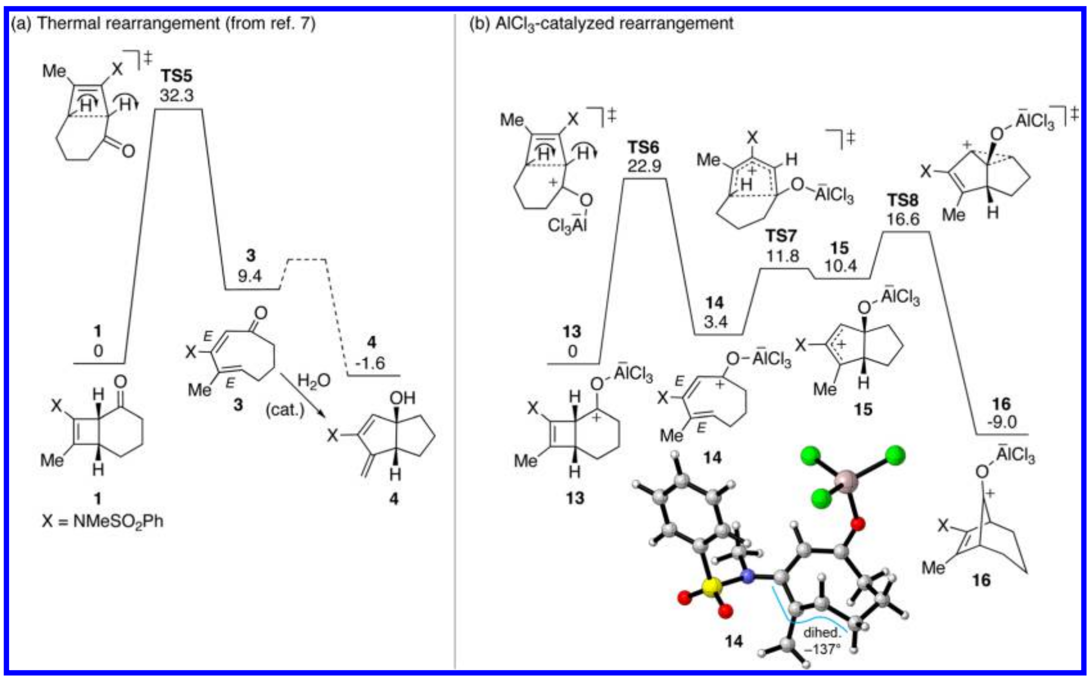

Figure 4. Free energy profiles for (a) thermal[7] and (b) $AlCl_3$-catalyzed rearrangements of 4,6-fused cyclobutenamide **1** in toluene, calculated at the M06-2X/6-311+G(d,p)//B3LYP/6-31G(d) level of theory with SMD solvent corrections. ΔG in kcal/mol.

available to the thermal reaction.[24,25] The availability of this downhill pathway explains why cycloheptadienone-derived products are obtained in the $AlCl_3$-catalyzed rearrangement of **2** but not in the thermal rearrangement.

Other Lewis acids, such as TMSOTf, BF_3-OEt_2, $TiCl_4$, Ti(*i*-PrO)$_2$Cl$_2$, $AlMe_2Cl$, $AlEtCl_2$, $CuCl_2$, Zn(OTf)$_2$, and $AgSbF_6$ were not effective in promoting the rearrangement of **2** to **8**. These Lewis acids gave only 2-amidodienes **5**, in very low yields, together with hydrolysis of the starting cyclobutenamide.[12] Traces of water are essential: when the reaction was performed in the presence of 4 Å molecular sieves, cyclobutenamide **2** was completely recovered. It is likely that traces of HCl are formed by hydrolysis, and the strong acid $HAlCl_4$ may play a role.

Calculations on the corresponding rearrangements of 4,6-fused cyclobutenamides **1** are shown in Figure 4. The $AlCl_3$-catalyzed rearrangement of **1** displays a qualitatively similar energy profile to that of **2** but has a smaller barrier ($\Delta G^{\ddagger}$ = 22.9 kcal/mol) and is more thermodynamically favored (ΔG = −9.0 kcal/mol). The product is a [3.2.1]-bicyclic ketone. Consistent with these theoretical findings, $AlCl_3$-catalyzed rearrangements of cyclobutenamides **1a−c** (Figure 5) were found experimentally to be cleaner reactions, giving [3.2.1]-bicyclic ketones **17a−c** in nearly quantitative yield. No 2-amidodienes analogous to **5** were obtained. In contrast to 4,5-fused

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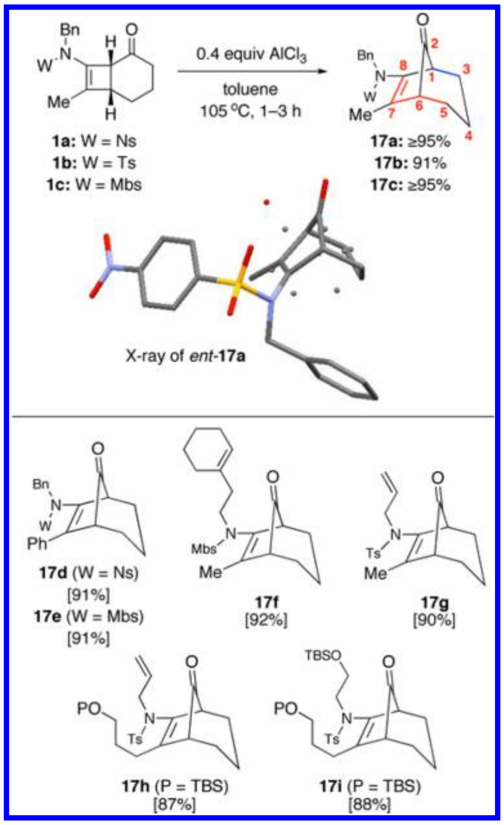

Figure 5. $AlCl_3$-catalyzed rearrangements of 4,6-fused cyclobutenamides 1 to [3.2.1]-bicyclic ketones 17.

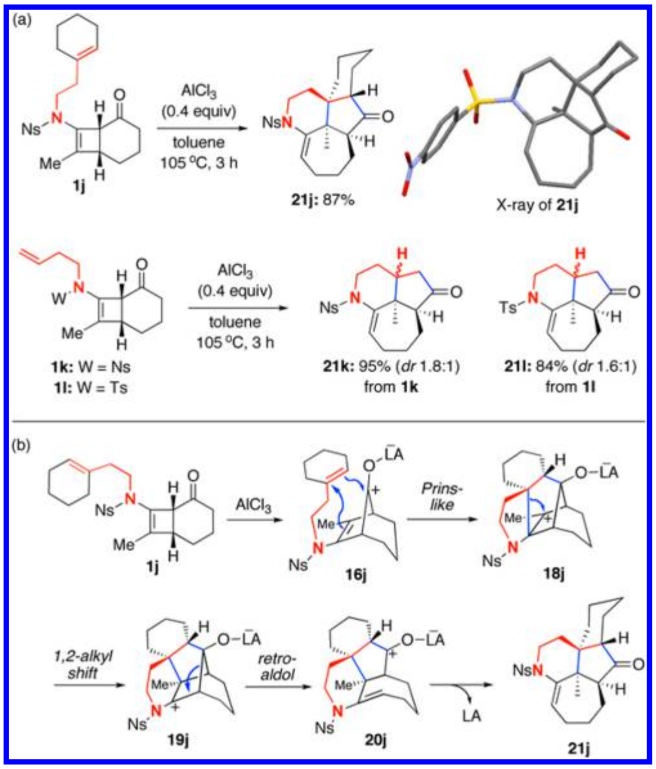

Figure 6. (a) Formation of tri- and tetracyclic products 21 from 4,6-fused cyclobutenamides 1. (b) Proposed mechanism for the cascade.

cyclobutenamides **2**, the rearrangements of **1** could also be catalyzed by other Lewis acids. Specifically, we found that BF_3-OEt_2 and $AlMe_2Cl$ were as effective as $AlCl_3$ in catalyzing the rearrangement of **1c** to **17c**,[12] while TMSOTf, Ti(*i*-PrO)$_2$Cl$_2$, Zn(OTf)$_2$, and $AgSbF_6$ afforded low to modest yields of **17c**. Compared with the rearrangements of **2**, the more facile rearrangements of **1** reflect the easier ring opening to the less strained, eight-membered cyclic dienones, and the lower energies of the TSs for the ensuing Nazarov-type cyclization and 1,2-alkyl shift. The generality of this transformation is exemplified by the high-yielding syntheses of bicyclic ketones **17d–i** from cyclobutenamides **1d–i** (Figure 5).

The $AlCl_3$-catalyzed rearrangement of **1j**, bearing a tethered alkene on nitrogen, did not give any of the expected bicyclic ketone **17j** but instead gave the complex aza-tetracycle **21j** in 87% yield (Figure 6). The structure of **21j** was unambiguously determined from its single-crystal X-ray structure. Calculations on this skeletal rearrangement (see the Supporting Information) mapped out a mechanism involving Prins-like cyclization of the tethered alkene onto bicyclic intermediate **16j**. Due to geometrical constraints imposed by the tether, the formation of the C–C bond between the alkene terminus and the carbocationic center occurs concomitantly with formation of a C–C bond between the substituted alkene carbon and the nitrogen-substituted carbon of the enamide [a formal (3 + 2) cycloaddition]. A 1,2-alkyl shift then gives **19j**, which undergoes retro-aldol ring opening to furnish the tetracyclic skeleton of **21j**. This cationic cascade does not apply to all types of tethered alkenes (see **17f–h** in Figure 5) but appears facile for certain cyclobutenamides containing a homoallyl group. Thus, aza-tricycles **21k** and **21l** were obtained in high yields from **1k** and **1l**, respectively (Figure 6). The Prins cascade did not take place with cyclobutenamide **1f**, however, where the rearrangement was arrested at ketone **17f**. Structurally, **1f** differs from **1j** (and **1k** and **1l**) by having a more electron-rich N-substituent (Mbs versus Ns or Ts). The cascade leading to aza-tri- and tetracycles **21** is rapid. For example, when the rearrangement of **1j** was performed in toluene-d_6 and monitored by NMR, **21j** was found to be formed within 10 min, with no detectable formation of [3.2.1]-bicyclic ketone **17j**.[26]

■ CONCLUSIONS

We have documented here the generation of highly strained seven- and eight-membered *cis,trans*-cycloalkadienones by $AlCl_3$-catalyzed ring opening of fused cyclobutenamides **2** and **1**, respectively. While cycloheptadienones had previously been theoretically predicted to be generated from **2** under thermal conditions,[7] the use of Lewis acidic conditions has allowed their reactivity to be studied for the first time. The bicyclic ketones derived from the novel Lewis acid-catalyzed rearrangements of **1** and **2** serve as excellent platforms for the synthesis of complex targets, as exemplified by the facile cascade syntheses of tri- and tetracyclic compounds **21**. It is noteworthy that such structural complexity can be generated in a one-pot operation from simple cyclobutenamides, which are themselves derived from straightforward [2 + 2] cycloadditions of enones with readily available ynamides.

■ EXPERIMENTAL SECTION

Rearrangement of 4,6-Fused Cyclobutenamides 1. To a flamed-dried sealed tube were added cyclobutenamide **1a** (58.7 mg, 0.14 mmol), toluene (2.1 mL, cyclobutenamide concn = 0.067 M) and $AlCl_3$ (1 M in nitrobenzene) (55.1 μL, 0.055 mmol) at rt. The reaction vessel was then capped and directly heated to 105 °C. After stirring at 105 °C for 1 h, the reaction mixture was cooled to rt slowly. The crude mixture was purified using silica gel flash column chromatography

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J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

(first using hexane to wash toluene away, and then isocratic eluent: 15% EtOAc in Hexane) to afford bicyclic ketone **17a** (57.0 mg, 0.13 mmol) in 97% yield.

Rearrangement of 4,5-Fused Cyclobutenamides 2. To a flamed-dried sealed tube were added cyclobutenamide **2a** (82.5 mg, 0.20 mmol), toluene (3.0 mL, cyclobutenamide concn = 0.067 M) and $AlCl_3$ (1.0 M in nitrobenzene: 80.0 μL, 0.080 mmol) at rt. The reaction vessel was then capped and directly heated to 105 °C. After stirring at 105 °C for 3.0 h, the reaction mixture was allowed to cool to rt slowly. The crude mixture was purified using silica gel flash column chromatography (first using hexane to wash toluene away, and then gradient eluent: 15% to 33% EtOAc in Hexane) to afford bicyclic ketone **8a** (56.1 mg, 0.14 mmol) in 68% yield and 2-amidodiene **5a**-Z^2 (8.6 mg, 0.021 mmol) in 10% yield.

Computational Methods. Geometry optimizations were performed in the gas phase at the B3LYP/6-31G(d) level of theory.[17] Vibrational frequency calculations indicated the nature of each stationary point (local minimum or first-order saddle point), and the computed frequencies were also used to derive unscaled zero-point energy and thermochemical corrections. Solvation energies were computed by means of single-point calculations with B3LYP/6-31G(d) in implicit toluene using the SMD continuum method.[19] Single-point energies were computed at the M06-2X/6-311+G(d,p) level of theory in the gas phase.[18] Free energies in solution were calculated by adding the B3LYP zero-point energy, thermochemical corrections, and solvation energy to the M06-2X potential energy. A standard state of 298.15 K and 1 mol/L was used.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, compound characterizations, NMR spectra, X-ray structural files, computational methods and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*e.krenske@uq.edu.au

*houk@chem.ucla.edu

*rhsung@wisc.edu

Present Address

¶Visiting Ph.D. student from Department of Chemistry, Oregon State University, 153 Gilbert Hall, Corvallis, Oregon 97331, United States.

Notes

The authors declare no competing financial interest.

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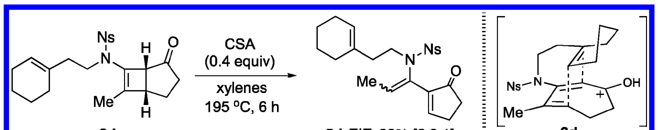
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

(13) 2-Amidodienes **5**-*Z* and **5**-*E* interconvert under the reaction conditions but do not fully equilibrate during the time scale of the synthetic experiments. The *Z*/*E* ratios depend on the rates of isomerization of **2** to **2**′-*trans*/*cis*, which are believed[7] to be rate-limiting.

(14) In an effort to trap any cycloheptadienone **6** that might be generated, we attempted an intramolecular Diels–Alder reaction starting from **2d** (see hypothetical DA transition state **6d**). However, only the normal 2-amidodienes **5d** (*Z*/*E*) were obtained (93%).



2d **5d**-*Z*/*E*: 93% [2.8:1] **6d**

(15) DFT calculations predict that ring opening of **2** to **5**-*Z* is favored by 4 kcal/mol ($\Delta\Delta G^{\ddagger}$) over opening to **5**-*E* (see the Supporting Information).

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(23) Decomplexation of $AlCl_3$ from **12** is uphill by 29 kcal/mol. However, in the catalytic cycle, product inhibition is avoided because complex formation between **2** and $AlCl_3$ is very favorable (−33 kcal/mol).

(24) It is not possible to quantitatively compare the rates of formation of **5** and **8**, because the step that is likely to be rate-determining in the formation of **5** (isomerization of **2** to **2**′) is catalyzed by traces of protic acid. However, the computed barriers for electrocyclic ring opening of **2**′-*trans* to **5**-*Z* and **2**′-*cis* to **5**-*E* (25.3 and 29.3 kcal/mol, respectively) are consistent with the experimentally observed exclusive *Z* selectivity in the formation of **5a**–**c** (see the Supporting Information).

(25) In our previous study[7] we concluded that traces of water are essential for the thermal rearrangement of **1** to **4**; specifically, a molecule of water acts a Brønsted acid catalyst of the Nazarov-like cyclization of **3** to **4**.

(26) Calculations indicate that the conversion of **16** to **20** (as the $AlCl_3$ complex) has $\Delta G^{\ddagger}$ = 15.7 kcal/mol and ΔG = −14.2 kcal/mol (see the Supporting Information).

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