Modular Synthesis of Azabicyclohexanes and Cyclobutenyl Amines

Kushal Dhake,[†§] Kyla J. Woelk,[†§] Joseph Becica,[†] Andy Un,[†] Sarah E. Jenny,[‡] and David C. Leitch[†]*

[†]Department of Chemistry, University of Victoria, 3800 Finnerty Rd., Victoria, BC V8P 5C2, Canada.
[‡]Department of Chemistry, Temple University, 1901 N. Broad St, Philadelphia, PA 19122, United States.

ABSTRACT: The development of two divergent and complementary Lewis acid catalyzed additions of bicyclobutanes to imines is described. Microscale high-throughput experimentation was integral to the discovery and optimization of both reactions. *N*-arylimines undergo formal (3+2) cycloaddition with bicyclobutanes to yield azabicyclo[2.1.1]hexanes in a single step; in contrast, *N*-alkylimines undergo an addition/elimination sequence to generate cyclobutenyl methanamine products with high diastereoselectivity. These new products contain a variety of synthetic handles for further elaboration, including many functional groups relevant to pharmaceutical synthesis. The divergent reactivity observed is attributed to differences in basicity and nucleophilicity of the nitrogen atom in a common carbocation intermediate, leading to either nucleophilic attack (*N*-aryl) or E1 elimination (*N*-alkyl).
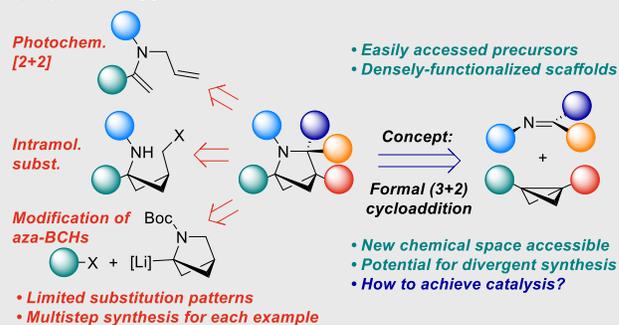
Rigid, conformationally-restricted Csp^3-based ring systems are becoming increasingly important as scaffolds and bioisosteres in small molecule drug candidates (Figure 1a).[1–7] Incorporating these topologically more complex architectures often improves the drug-like properties of the resulting molecules, such as solubility, lipophilicity and metabolic stability;[8–11] however, accessing many candidate structures remains difficult due to a lack of general, reliable, and modular synthetic methods.[12–14] This is especially true for 2-azabicyclo[2.1.1]hexanes (aza-BCHs) where synthesis relies on intramolecular cyclization of prefunctionalized substrates,[14–18] or stepwise functionalization of existing aza-BCHs[19–21] (Figure 1b). These methods are limited with respect to modular synthesis of highly functionalized systems, which is required for medicinal chemistry SAR exploration.

As an alternative retrosynthetic concept, we postulated that aza-BCHs could be accessed via formal (3+2) cycloaddition between bicyclobutanes[22–28] and imines, analogous to the reactivity of donor-acceptor cyclopropanes[29–31] (Figure 1b). This approach would directly generate highly substituted aza-BCHs in a modular fashion, using readily available imines and bicyclobutanes as building blocks. Here, we show that Lewis acid catalysis enables divergent reactivity between imines and bicyclobutanes, giving two classes of densely-functionalized amine products. With *N*-aryl imines, the envisioned cycloaddition leads to a variety of aza-BCHs under mild conditions. In contrast, *N*-alkyl imines react diastereoselectively to give cyclobutenyl methanamines as the major product (Figure 1c). Synthesis of highly-substituted and stereochemically-defined cyclobutyl scaffolds is often challenging.[32–34] This imine addition to bicyclobutanes, complementary to aza-BCH formation, gives rise to structurally complex cyclobutenes that have multiple points for further functionalization. Both of these amine product classes are potentially valuable additions to the growing set of Csp^3-rich scaffolds being investigated in medicinal chemistry.[35]
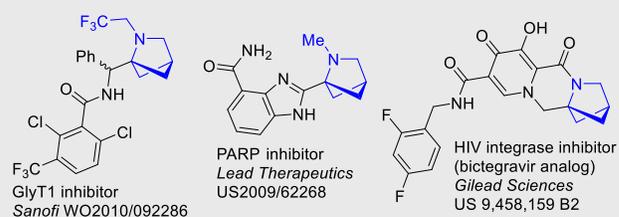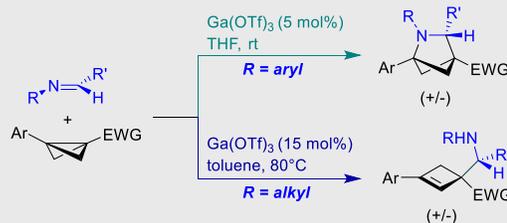

Figure 1. a) Potential of azabicyclo[2.1.1]hexanes (aza-BCHs) as structural elements in medicinal chemistry; **b)** synthetic challenges in existing approaches and new retrosynthetic concept; **c)** divergent access to azabicyclohexanes and cyclobutenyl methanamines.
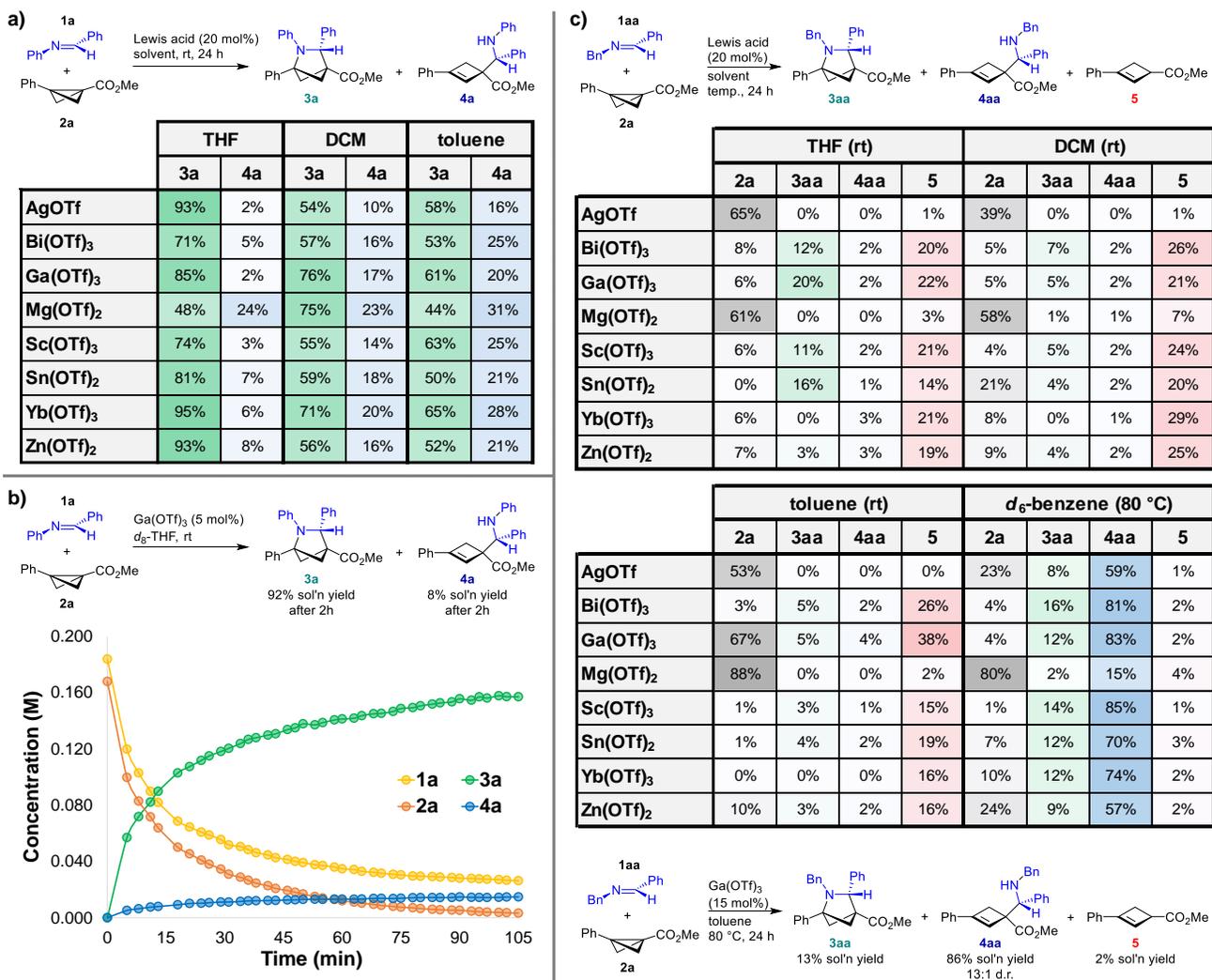
Figure 2. a) Microscale high-throughput screening results (solution yields) for the Lewis acid catalyzed addition of *N*-phenyl imine **1a** to bicyclobutane **2a**, revealing azabicyclohexane **3a** as the major product and cyclobutenyl methanamine **4a** as a minor product; **b)** reaction progress plot with Ga(OTf)₃ (5 mol%) as catalyst, indicating both products are formed in parallel pathways; **c)** microscale high-throughput screening results (solution yields) for the Lewis acid catalyzed addition of *N*-benzyl imine **1aa** to **2a**, revealing formation of cyclobutenyl methanamine **4aa** as the major product at elevated temperature in d_6-benzene, and confirmation of product distribution using Ga(OTf)₃ (15 mol%) in toluene at 80 °C. All solution yields are obtained by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

Figure 2a table:

	THF		DCM		toluene	
	3a	4a	3a	4a	3a	4a
AgOTf	93%	2%	54%	10%	58%	16%
Bi(OTf)₃	71%	5%	57%	16%	53%	25%
Ga(OTf)₃	85%	2%	76%	17%	61%	20%
Mg(OTf)₂	48%	24%	75%	23%	44%	31%
Sc(OTf)₃	74%	3%	55%	14%	63%	25%
Sn(OTf)₂	81%	7%	59%	18%	50%	21%
Yb(OTf)₃	95%	6%	71%	20%	65%	28%
Zn(OTf)₂	93%	8%	56%	16%	52%	21%

Figure 2c tables:

	THF (rt)				DCM (rt)			
	2a	3aa	4aa	5	2a	3aa	4aa	5
AgOTf	65%	0%	0%	1%	39%	0%	0%	1%
Bi(OTf)₃	8%	12%	2%	20%	5%	7%	2%	26%
Ga(OTf)₃	6%	20%	2%	22%	5%	5%	2%	21%
Mg(OTf)₂	61%	0%	0%	3%	58%	1%	1%	7%
Sc(OTf)₃	6%	11%	2%	21%	4%	5%	2%	24%
Sn(OTf)₂	0%	16%	1%	14%	21%	4%	2%	20%
Yb(OTf)₃	6%	0%	3%	21%	8%	0%	1%	29%
Zn(OTf)₂	7%	3%	3%	19%	9%	4%	2%	25%

	toluene (rt)				d_6-benzene (80 °C)			
	2a	3aa	4aa	5	2a	3aa	4aa	5
AgOTf	53%	0%	0%	0%	23%	8%	59%	1%
Bi(OTf)₃	3%	5%	2%	26%	4%	16%	81%	2%
Ga(OTf)₃	67%	5%	4%	38%	4%	12%	83%	2%
Mg(OTf)₂	88%	0%	0%	2%	80%	2%	15%	4%
Sc(OTf)₃	1%	3%	1%	15%	1%	14%	85%	1%
Sn(OTf)₂	1%	4%	2%	19%	7%	12%	70%	3%
Yb(OTf)₃	0%	0%	0%	16%	10%	12%	74%	2%
Zn(OTf)₂	10%	3%	2%	16%	24%	9%	57%	2%

Initial reaction discovery was enabled by microscale high-throughput screening using a combination of solvents and Lewis acids for the coupling of imine substrates (**1a** and **1aa**) and bicyclobutane **2a** (Figure 2).[36,37] A multivariate design allowed us to evaluate all combinations between Lewis acid identity and solvent to account for possible interaction effects.[38] For *N*-aryl imine **1a**, catalysis at room temperature forms both the desired aza-BCH **3a** and the corresponding cyclobutenyl methanamine **4a** (Figure 2a). The **3a** to **4a** ratio depends mainly on solvent, with THF giving 2-to-10-fold less **4a** than DCM and toluene. Every Lewis acid screened gives similar reaction outcomes except for Mg(OTf)₂, which gives a higher amount of **4a** even in THF. Among the catalysts tested, AgOTf and Ga(OTf)₃ give the smallest amount of **4a**; evaluating these two catalysts at lower loading (5 mol%) revealed Ga(OTf)₃ as superior.[39]

To understand the origin of the product distribution, we monitored reaction progress using *in situ* ¹H NMR spectroscopy (Figure 2b). We observe excellent mass balance for the conversion of **1a**/**2a** into the **3a**/**4a** mixture, with a constant **3a**:**4a** ratio of 11:1 throughout the reaction, and a 92% solution yield of **3a**

after 2h. This reaction profile is consistent with **3a** and **4a** being formed in parallel pathways that share a common intermediate.

In contrast to **1a**, productive reactions of *N*-alkyl imine **1aa** with **2a** did not readily proceed at room temperature, regardless of the Lewis acid/solvent combination (Figure 2c). Instead, we observe generally poor mass-balance, and significant amounts of the cyclobutene side product **5**. In select cases with THF solvent, we do observe the aza-BCH **3aa** in low yield (12-20%). In an attempt to improve the reaction outcome, we assessed an elevated temperature (80 °C) using d_6-benzene. Under these conditions, we observe a complete reversal of chemoselectivity to give the cyclobutenyl methanamine **4aa** as the major product, with Ga(OTf)₃ again among the best catalysts. This microscale result was confirmed using Ga(OTf)₃ (15 mol%), giving **4aa** in 86% solution yield with a d.r. of 13:1. We assessed the possibility of **4aa** formation by ring-opening elimination of **3aa**,[40,41,42] as well as **3aa** formation by intramolecular hydroamination[43] of **4aa** (eq. 1). Heating isolated **3aa** or **4aa** in the presence of Ga(OTf)₃ led to no observable conversion, consistent with parallel reaction pathways for **3aa**/**4aa** formation.

$$\text{(1)}$$
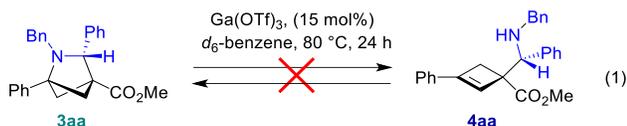
During our efforts to scale-up the synthesis of both **3a** and **4aa**, we initially observed small yet variable amounts of the cyclobutene **5** as a side product. To elucidate the factors that contribute to its formation, we conducted a series of control experiments on the bicyclobutane **2a** (Table 1). While **2a** is stable in solution (d_6-benzene or THF) at room temperature over extended time periods, heating **2a** in d_6-benzene over 24 h gives 67% solution yield of **5** (entry 1). This extent of thermal decomposition is not consistent with the observed product distribution for the formation of **4aa** during catalysis under optimized conditions. In striking contrast, heating a solution of **1aa** and **2a** – a no-catalyst control experiment – leads to no observable reaction (entry 2). Mixing **2a** with Ga(OTf)$_3$ in d_6-benzene (entry 3) or THF (entry 4) leads to near immediate and complete conversion of **2a** into **5**. Perplexingly, addition of **1a** or **1aa** into the mixtures from entries 3 and 4 represents the optimized catalytic reaction conditions from Figure 2, where we observe very little (or no) **5**.

Table 1. Decomposition of **2a** into cyclobutene **5**.

Entry	Conditions	Yield **5** (%)[b]
1	d_6-benzene, 80 °C, 24 h	67
2	**1aa** (1.5 equiv) d_6-benzene, 80 °C, 24 h	n.r.[b]
3	Ga(OTf)$_3$ (15 mol%), d_6-benzene, rt, 20 min	>95
4	Ga(OTf)$_3$ (5 mol%), THF, rt, 20 min	>95
5	2,6-lutidine (1.5 equiv), d_6-benzene, 80 °C, 24 h	n.r.[b]
6	2,6-lutidine (1.5 equiv), Ga(OTf)$_3$ (15 mol%), d_6-benzene, 80 °C, 24 h	n.r.[b]
7	2,6-lutidine (1.1 equiv), Ga(OTf)$_3$ (5 mol%), THF, rt, 24 h	n.r.[b]

[a]Determined by ^{1}H NMR spectroscopy versus internal standard (1,3,5-trimethoxybenzene). [b]n.r. = no reaction (**5** not observed, >95% **2a** remaining).

These results are consistent with decomposition of **2a** being mediated by trace Brønsted acid, and that the imine substrate quenches this acid to inhibit decomposition during catalysis. To test this hypothesis, we carried out additional control experiments similar to those from entries 1, 3, and 4, but with the addition of 2,6-lutidine to emulate the basicity of the imine substrate (entries 5-7). In every case, no reaction occurs, leaving **2a** intact. Not only do these experiments reveal the probable source of bicyclobutane-to-cyclobutene isomerization as trace acid, it also reveals a key practical aspect of reaction order-of-addition: the Lewis acid catalyst must be added last to prevent rapid bicyclobutane decomposition.

Using the two sets of reaction conditions from Figure 2, we explored the scope of aza-BCHs (Method A) and cyclobutenyl

methanamines (Method B) accessible from imines and bicyclobutanes containing a variety of pharmaceutically-relevant substituents and functional groups (Figure 3). Using Method A, compound **3a** is isolated in 86% yield on 1 mmol scale. Increasing steric bulk on the imine *N*-aryl group with *o*-tolyl (**3b**) and 2-naphthyl (**3c**) substituents is compatible with the chemistry, though incorporating a 2,6-methylphenyl group at nitrogen leads to no reaction. Electron donating (**3d**, **3e**) and withdrawing groups (**3f**, **3g**, **3h**) on the *N*-aryl ring are also compatible, providing substituents for further functionalization.

A series of multisubstituted *N*-aryl imines are also successful, including those with electron donating and withdrawing groups on both aryl rings (**3i**, **3j**), 5- and 6-membered heterocycles (**3k-3o**), and halides (**3l**, **3m**). Particularly noteworthy is **3l**, which contains Ar–I and 2-Cl-pyridyl moieties available for further functionalization; importantly, we observe no competing reactivity at the electrophilic 2-Cl-pyridyl group. Finally, alternative aryl and electron withdrawing groups on the bicyclobutane are compatible, including *p*-F-phenyl (**3p**), primary (**3q**), secondary (**3r**), and tertiary (**3s**) alkyl esters, and morpholine amide (**3t**). Unfortunately, a menthyl ester provides no stereoinduction (**3r** is isolated with 1.4:1 d.r.). In some cases, we observe the corresponding cyclobutenyl methanamines (**4**) as minor products that co-elute with the aza-BCHs (**3**) during chromatography (**3/4d**, **k**, **n**, **o**, and **s**).

For *N*-alkyl imine substrates, Method B gives a variety of cyclobutenyl methanamines (Figure 3, right), with the pictured diastereomer as the major product; the relative stereochemistry shown is assigned based on NMR characterization of the iodoamination products (*vide infra*). In all cases, we prioritized enriching the major diastereomer during purification rather than seeking maximum chemical yield. Compound **4aa** is isolated in 66% yield with increased stereopurity after purification (d.r. = 27:1 versus 11:1 initially). A *p*-methoxybenzyl (PMB) group is compatible, providing an acid-labile protecting group for nitrogen (**4bb**). Increased steric bulk at nitrogen, including cyclohexyl and *tert*-butyl groups (**4cc**, **4dd**), leads to lower yield but improved diastereoselectivity; for **4cc**, challenges with isolation by column chromatography are partly responsible for the low yield (43% NMR yield versus 19% isolated). Several *C*-aryl groups are also compatible, including 1-naphthyl (**4ee**) and various heterocycles (**4ff-4ii**). Notably, unsubstituted 5-membered heterocycles (**4ff** and **4gg**) give decreased diastereoselectivity relative to phenyl, though the larger 1,3-dimethylpyrazolyl product (**4hh**) is formed in 13:1 d.r. (17:1 after purification). A 2-Cl-pyridyl group can also be incorporated (**4ii**).

Using (*S*)-α-methylbenzyl as a chiral auxiliary at nitrogen leads to only two of the four possible stereoisomers being observable by NMR, with the major stereoisomer formed with 6-7:1 d.r. (**4jj-4ll**). The absolute stereochemistry pictured is assigned based on 2D NOESY analysis of **6jj** (*vide infra*). We have also isolated the minor diastereomer of **4ll**, confirming by 2D NOESY that it possesses the same relative stereochemistry as the major diastereomer at the two new stereogenic centers.[39] In other words, the observed diastereoselectivity is controlled by the (*S*)-α-methylbenzyl chiral auxiliary. Finally, bicyclobutanes with alternative aryl and electron withdrawing groups are compatible (**4mm-4pp**); in the case of **4mm**, we observe the corresponding aza-BCH (**3mm**) as a co-eluting minor product. As for **3r**, a menthyl ester in **4pp** provides effectively no stereoinduction, with two major (~3:2 ratio) and two minor diastereomers observed by NMR spectroscopy.
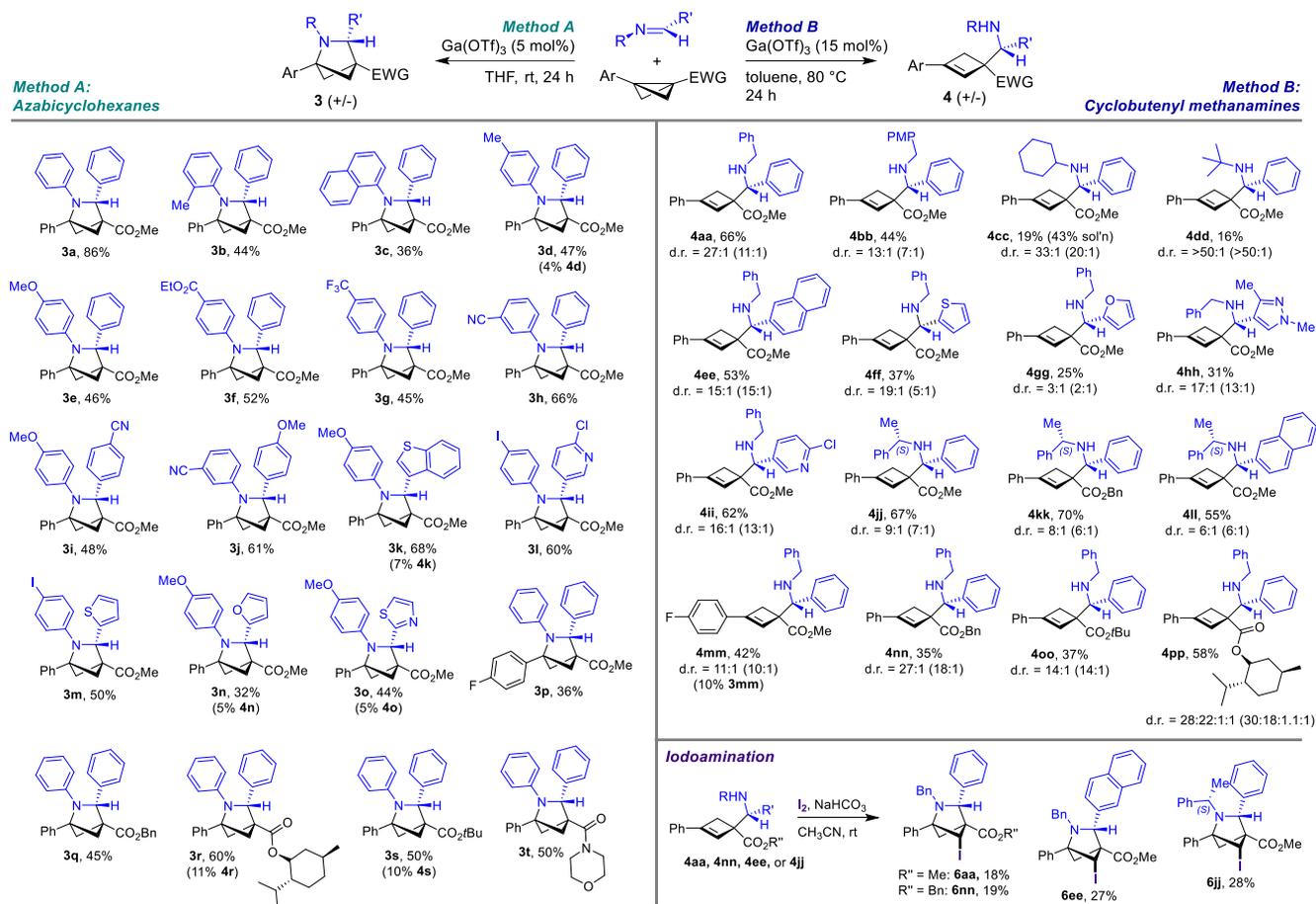
Figure 3. Scope of the divergent reactions using *N*-aryl imines (Method A) and *N*-alkyl imines (Method B); d.r. values in parentheses determined by ^{1}H NMR spectroscopy of crude products prior to purification. Selected cyclobutenyl methanamine products were converted to azabicyclohexanes via an iodoamination reaction, yielding single diastereomers with four contiguous stereocenters. The relative stereochemistry of **6aa** was determined by 2D NOESY, enabling assignment of the relative stereochemistry of the cyclobutenyl methanamine products by analogy; the absolute stereochemistry of **6jj** was similarly assigned by 2D NOESY (see Supporting Information for further details on stereochemical assignment).
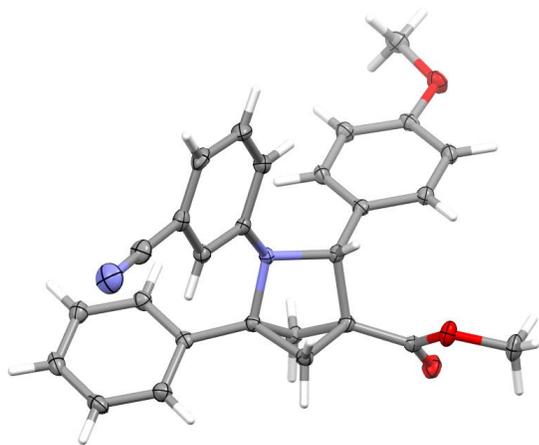

Figure 4. Solid-state molecular structure of **3j** (ellipsoids plotted at 50% probability, enantiomer of **3j** from extended structure not shown for clarity). See SI for metrical parameters.

To demonstrate potential synthetic applications of these cyclobutenes, and to generate conformationally rigid products for stereochemical assignment by 2D NOESY,[39] we converted four cyclobutenes into aza-BCHs (**6aa**, **6ee**, **6jj**, **6nn**) using a general

and unoptimized iodoamination reaction. Taking advantage of iodonium formation on the opposite side of the cyclobutene to the methanamine substituent enables formation of diastereomerically pure products containing four contiguous stereocenters, two of which are tetrasubstituted. Thus, this iodoamination reaction enables access to complex *N*-alkyl aza-BCHs with several points for potential functionalization. The relative stereochemistry for **6aa** was established using 2D NOESY; a correlation is observed between the methine hydrogen α to nitrogen and the hydrogen attached to the same carbon as the iodine, clearly indicating these two protons are on the same side of the azabicyclohexane ring.[39] Using (*S*)-α-methylbenzyl as a chiral auxiliary gives **6jj** with defined absolute configuration, which we also determined by 2D NOESY. Key correlations between the α-methylbenzyl hydrogens and the hydrogens on the azabicyclohexane ring are consistent with the pictured absolute stereochemistry.[39]

To rationalize the divergent reaction pathways leading to aza-BCH or cyclobutene formation, we propose the general mechanism shown in Figure 5a, which shares aspects of prior proposals for the addition of strongly electron deficient ketones or alkenes to bicyclobutane[44] and 1-azabicyclobutane[45] substrates. In this proposal, the initial reaction between bicyclobutane and imine proceeds through Lewis acid induced enolate formation

at the bicyclobutane; this Lewis acid activation is consistent with the rapid isomerization of **1a** to **5** in the absence of imine (Table 1). Subsequent C–C bond formation between this enolate and the imine (which could also be activated by coordination to the Lewis acid) affords the carbocation species **7**. This key intermediate could then undergo either a ring-closing nucleophilic attack by nitrogen onto the carbocation, or an intramolecular E1 elimination. The relative rates of these two pathways will be controlled by the kinetic nucleophilicity versus basicity of the nitrogen atom: for *N*-aryl groups, the nitrogen is more nucleophilic than basic, whereas *N*-alkyl are more basic than nucleophilic. This parallel mechanism is also consistent with the simultaneous formation of **3a** and **4a** (Figure 2b) and the inability for **3aa** and **4aa** to interconvert under the reaction conditions (eq. 1).

To explain the observed diastereoselectivity for the synthesis of cyclobutenyl methanamines (**4**), we propose the stereochemical model in Figure 5b. The major and minor diastereomers are differentiated by whether H_a or H_b undergoes elimination. As-drawn, a clockwise (CW) bond rotation to remove H_b will lead to higher torsional strain due to the eclipsing interaction between the *C*–R' group and the electron-withdrawing group on the cyclobutane. In contrast, a counter clockwise (CCW) bond rotation to remove H_a requires less torsional strain, leading to the major observed diastereomer. Work is underway to further elucidate the operative mechanistic pathways.
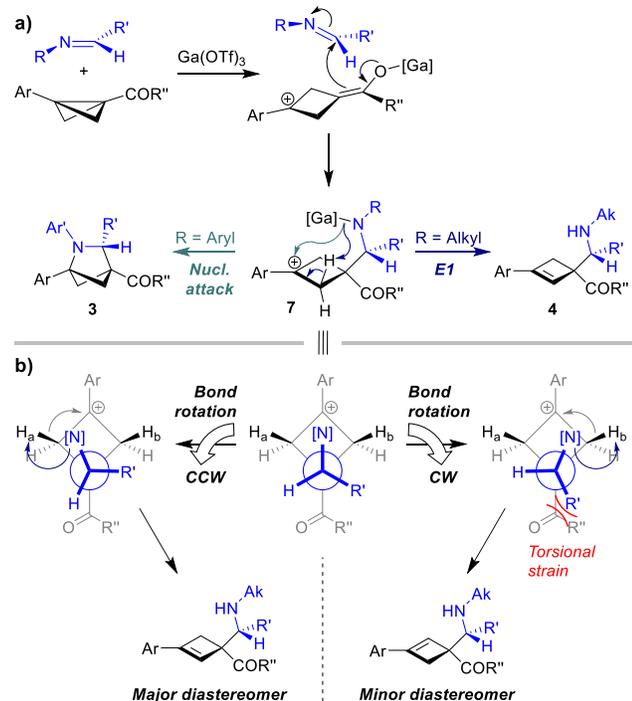

Figure 5. a) Proposed pathways for the formation of **3** and **4** from a common carbocation intermediate; **b)** stereochemical model for the observed relative stereochemistry in cyclobutenyl methanamine formation (CW = clockwise; CCW = counterclockwise).

In summary, we have developed two complementary approaches to the functionalization of bicyclobutanes by exploiting the divergent reactivity exhibited by *N*-aryl and *N*-alkyl imines under Lewis acid catalysis. The resulting products provide a unique platform for chemical space exploration in pursuit of new, C*sp*^{3}-rich drug candidates, especially given the func-

tional group compatibility exhibited with respect to heterocycles and diverse synthetic handles. Work is ongoing to explore the mechanistic and synthetic features of this chemistry, and to apply these techniques toward complex molecule synthesis relevant to the discovery of active pharmaceutical ingredients.

ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, full tables of screening data, characterization data for new compounds, and X-ray crystallography details. The CIF for **3k** is deposited with the CCDC with deposition number 2103579.

AUTHOR INFORMATION

Corresponding Author
*dcleitch@uvic.ca

Author Contributions
§These authors contributed equally.

Notes
The authors declare no competing financial interest.

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