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Synthesis of 3-benzazepines and azepino[4,5-*b*]heterocyclic ring systems via intramolecular Friedel–Crafts cyclization

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ABSTRACT

The intramolecular Friedel–Crafts cyclization was found to be effective for the synthesis of 3-benzazepines and azepino[4,5-*b*]heterocyclic ring systems using simple allylic bromides tethered to activated aromatic nuclei. Amongst the various Lewis acids screened, $Bi(OTf)_3$ was found to be the most effective 'ecofriendly' catalyst for the cyclization.

Alkaloids containing seven-membered ring core scaffolds are found in many natural products and biologically active compounds,[1] and the substituted 3-benzazepine motif in particular has been exploited as a scaffold for potential medicinal agents in several therapeutic applications. Representative examples are shown in Figure 1 that include azepino[4,5-*b*]indole FXR agonists **1**,[2] 3-benzazepine dopamine agonist SCH23390 (**2**),[3] the natural product 3-benzazepine (±)-cephalotaxine (**3**),[4] and azepino[4,5-*b*]indole arboflorine (**4**).[5] Consequently, significant synthetic efforts have been devoted to the development of efficient protocols for the preparation and direct functionalization of these fused cyclic heteroaromatics. Many of these include intramolecular extensions of Friedel–Crafts-type approaches[6] and Tsuji–Trost/Heck reactions,[7] as well as radical cyclizations[8] and thermal rearrangement-promoted cyclizations,[9] among others.[10]

The development of useful methods for the formation of nitrogen-containing seven-membered rings can constitute a greater challenge than for smaller ring homologs due to entropic factors in the ring closure, and increased ring strain in the corresponding cyclic products.[11] The efficiency of intramolecular Friedel–Crafts (IMFC)-type reaction chemistry in particular often suffers from relevant drawbacks such as the lack of regioselective control in the cyclization step, and the typical need for high reaction temperatures and stoichiometric amounts of Lewis acid catalysts, some of which generate metal-containing waste streams of environmental concern.[6] Keeping all of these drawbacks in mind, we set out to develop a thermally mild IMFC method to prepare 3-benzazepines and azepino[4,5-*b*]heterocyclic rings that was both regioselective and catalytic in an ecologically benign activating reagent.[12]

We initially envisioned the synthesis of azepino[4,5-*b*]hetereoaromatic systems through an IMFC reaction utilizing catalytic amounts of an environmentally friendly metal. Inspired by the reports of Cook and coworkers that demonstrated a remarkably mild $InCl_3$-catalyzed Friedel–Crafts cyclization utilizing both electron-rich and electron-poor arene substrates,[13] we started

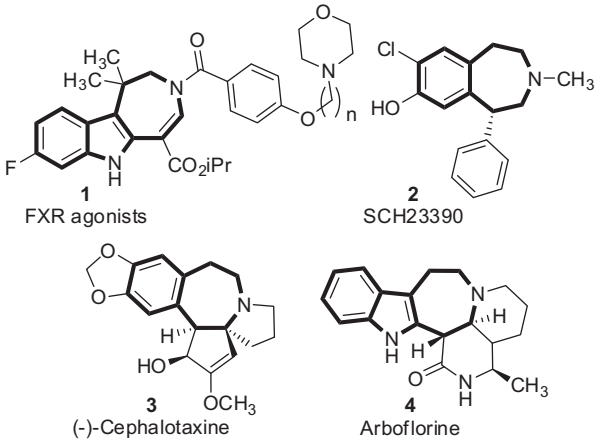

Figure 1. Examples of 3-benzazepine and azepino[4,5-*b*]heterocyclic bioactive agents and natural products.

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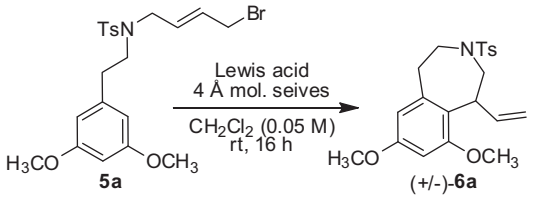
Table 1
Lewis acid catalyst screening reactions



Entry	Lewis acid	Yield
1	$InCl_3$ (20 mol %)	0[a]
2	$InCl_3$ (50 mol %)	0[a]
3	$InCl_3$ (100 mol %)	>98%[b]
4	$InBr_3$ (20 mol %)	Trace[a]
5	In(0) (20 mol %)	0[a]
6	$Ag_2O{\cdot}4B_2O_3$ (20 mol %)	40%[c]
7	AgOTf (20 mol %)	23%[c]
8	$ZnCl_2$ (20 mol %)	Trace[a]
9	$FeCl_3$ (20 mol %)	Trace[a]
10	$TiCl_4$ (20 mol %)	Trace[a]
11	$SnCl_4$ (20 mol %)	71%[c]
12	$Bi(OTf)_3$ (20 mol %)	>98%[b]
13	$Bi(OTf)_3$ (20 mol %)	33%[b,d]
14	$Bi(OTf)_3$ (100 mol %)	>98%[b,e]
15	$BiCl_3$ (20 mol %)	57%[c]
16	$BiBr_3$ (20 mol %)	44%[c]
17	$Bi(NO_3)_3{\cdot}5H_2O$ (20 mol %)	18%[c]
18	Bi(0) (20 mol %)	0[a]

[a] Starting material recovered.
[b] Isolated yield.
[c] NMR yield using 1,2,3-trimethoxybenzene as an internal standard.
[d] Run without 4 Å molecular sieves.
[e] Run without 4 Å molecular sieves, but 1 equiv of Hunig's base added.

our investigation by employing this In(III) salt. As a test case, we sought to induce the cyclization of allylic bromide **5a** to vinyl-substituted 3-benzazepine **6a** (Table 1). Unfortunately, our first attempts with catalytic $InCl_3$ in dichloromethane at room temperature failed to facilitate the reaction even with 50 mol % (entries 1 and 2), although a full equivalent was successful in affording **6a** in almost quantitative yield (entry 3). The use of $InBr_3$ also failed to induce cyclization at 20 mol %, as did indium metal itself (entries 4 and 5).

A survey to identify a more suitable alternative found that the reaction was promoted to varying degrees by a few other Lewis acids. Silver salts $Ag_2O{\cdot}4B_2O_3$ and AgOTf did afford low amounts of product, with the balance of starting material **5a** converted into byproducts (Table 1, entries 6 and 7). Application of $ZnCl_2$, $FeCl_3$, and $TiCl_4$ to the reaction resulted in only trace amounts of product, with full recovery of unreacted starting material (entries 8–10). Although a catalytic amount of $SnCl_4$ was effective in promoting the reaction (entry 11), it was not selected for use due to its toxicity issues.[14] A number of other common Lewis acids also failed to promote the IMFC reaction (data not shown, see Supplementary data).

The utility of bismuth(III) salts has attracted recent attention due to their low toxicity, low cost, and good stability and demonstrated high catalytic efficiency, rendering them suitable Lewis acids for green chemistry.[15] Their use in Lewis acid-promoted addition of aromatic nucleophiles to electron-deficient alkenes made it a natural choice to facilitate our system. We were therefore pleased to find that 20 mol % of $Bi(OTf)_3$ was equally as effective as 100 mol % of $InCl_3$ (Table 1, entries 12 vs 3), providing **6a** from **5a** in almost quantitative isolated yield. It was interesting to note that the efficacy drops off significantly in the absence of molecular sieves, providing only 33% yield and substantial decomposition byproducts (entry 13). In a simple experiment to probe whether the molecular sieves perform the role of an acid scavenger,[16] we subjected **5a** to conditions without molecular sieves, but with full equivalents of both $Bi(OTf)_3$ and Hunig's base, from which **6a** was obtained in 98% yield (entry 14).

The other available bismuth(III) salts $BiBr_3$ and $Bi(NO_3)_3{\cdot}5H_2O$ were much less effective than $Bi(OTf)_3$ (Table 1, entries 16 and 17) and the use of bismuth metal was completely ineffective (entry 18). It should also be noted that the reaction proceeded well in non-coordinating solvents such as chloroform, toluene, 1,2-dichloroethane, and hexane, but failed to provide significant product amounts in solvents possessing donor heteroatoms such as acetonitrile, THF, 1,4-dioxane, or methanol (see Supplementary data for more details).

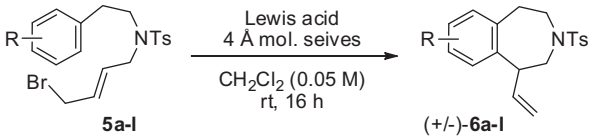
With promising reaction conditions in hand, we next explored a limited substrate scope for the IMFC reaction with allylic bromide-tethered precursors **5a–l** (Table 2).[17] Good to moderate yields were obtained utilizing 20 mol % of $Bi(OTf)_3$ with several substrates bearing electron-rich aromatic moieties (entries 1 through 7). In these cases where symmetrically-substituted aromatic nuclei (relative to the alkylamine functionality) were employed (e.g., **5a**, **5d**, and **5e**), single products were obtained (entries 1, 4, and 5). For unsymmetrically-substituted aryl substrates (e.g., **5b**, **5c**, **5f**, and **5g**), regioisomeric mixtures of products were obtained, often in preference for the products of the *para*-directing substitution of the electron-donating moiety (*para*-products of entries 2, 3, 6, and 7). In general, substrates with alkoxy-substituted groups gave excellent yields (entries 1–4) compared to precursors with the weaker electron-donating methyl functionality (entries 5–7), which required increased catalyst loading to perform efficiently.

In comparison, the relatively electron-neutral precursor **5h** was less favorable for the cyclization reaction (entry 8), whereas the electron-withdrawing effect of the 4-chlorophenyl substrate **5i** did not provide the corresponding 3-benzazepine adduct **6i**, and led only to trace amounts of product with a full loading of Lewis acid (entry 9). Interestingly, the presence of a cyclopropyl group in precursor **5j** led to an improvement in yield versus parent substrate **5h** (entry 10 vs 8), possibly due to a favorable conformation induced by sterics in the transition state, allowing better access to the geometry required for the cyclization reaction.

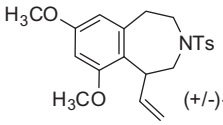
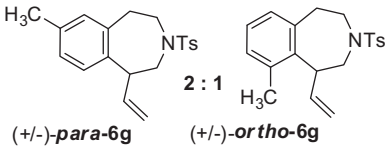
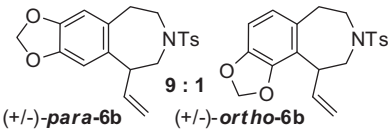
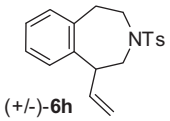
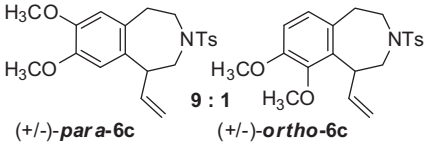
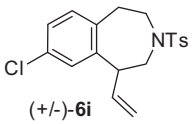
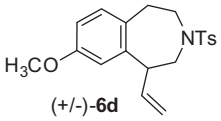
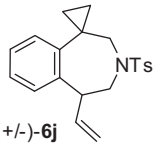
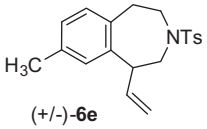
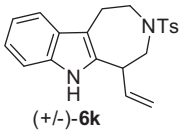
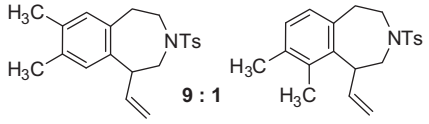
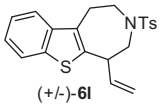
We were pleased to find that heterocyclic precursors provided excellent yields of azepino[4,5-*b*]heterocycles when conducted below room temperature (entries 11 and 12). Both indole **5k** and benzothiophene **5l** were shown to react at the C2 position to provide the corresponding products in near-quantitative isolated yields, and it is important to note that no protection of the indole nitrogen atom was necessary (entry 11).

These results clearly indicate that the cyclization requires an electron rich aromatic ring to afford good efficiency to provide the 3-benzazepine ring system, findings which are congruent with the recent results of Inui and coworkers toward the synthesis of 2-benzazepines.[18] On the basis of these findings, we suggest a reaction mechanism as depicted in Figure 2, in which the coordination of the bismuth metal to the allylic functionality can lead to two distinct modes of activation. First, the Lewis acid may activate the allylic moiety by coordinating to both the olefin π-system as well as to the bromide to generate a neutral intermediate **7a** or continue to displace the halide leading to an ionic species **7b**. Supposing a pre-organization of the linear molecule into a boat-chair type conformation, transition through either **7a** or **7b** allows electrophilic addition placing the newly-formed vinylic substituent in a pseudo-equatorial disposition. One could expect that electron-donating substitution on the aromatic ring would better stabilize the cationic cyclization adduct **8**, which facilitates rearomitization to generate the desired aryl-fused seven-membered ring product **6**.[19] This mechanism may also explain the detrimental effect of donor atom-containing solvents on this IMFC reaction. Some mechanistic investigations are in progress in order to better define the mode of this unprecedented cyclization.

Table 2
$Bi(OTf)_3$-catalyzed IMFC formation of 3-benzazepines and azepino[4,5-*b*]heterocyclic ring systems **6**[a]



5a-l (+/-)-**6a-l**

Entry	Product	Yield[b]	Entry	Product	Yield[b]
1	 (+/-)-**6a**	98%	7	 (+/-)-***para*-6g** **2 : 1** (+/-)-***ortho*-6g**	60% (78%)
2	 (+/-)-***para*-6b** **9 : 1** (+/-)-***ortho*-6b**	75% (98%)	8	 (+/-)-**6h**	30% (55%)
3	 (+/-)-***para*-6c** **9 : 1** (+/-)-***ortho*-6c**	72% (95%)	9	 (+/-)-**6i**	0 (Trace)
4	 (+/-)-**6d**	65% (88%)	10	 (+/-)-**6j**	65% (89%)
5	 (+/-)-**6e**	50% (77%)	11	 (+/-)-**6k**	98%[c]
6	 (+/-)-***para*-6f** **9 : 1** (+/-)-***ortho*-6f**	62% (82%)	12	 (+/-)-**6l**	98%[c]

[a] $Bi(OTf)_3$ (20 mol %), 4 Å molecular sieves, CH_2Cl_2 (0.05 M), rt, 16 h.
[b] Yield of isolated product; yield in parenthesis indicates reaction with 1 equiv of $Bi(OTf)_3$.
[c] Reaction carried out at 0 °C.

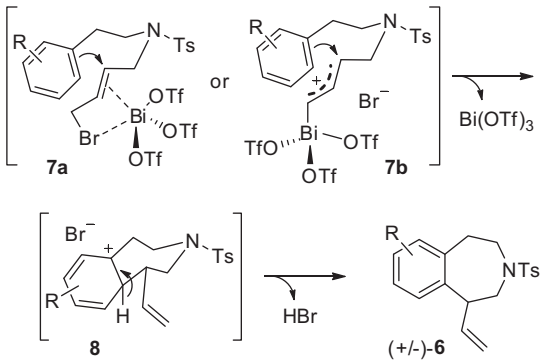


Figure 2. Proposed modes of cyclization.

In conclusion, we have defined a mild intramolecular Friedel–Crafts cyclization (IMFC) catalyzed by an environmentally benign Bi(III) salts for the preparation of 3-benzazepines products and their corresponding azepino[4,5-*b*]heterocyclic congeners. Some mechanistic investigations are in progress in order to better understand the mode of cyclization, and extension to an asymmetric variant to this transformation will be communicated in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.012.

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16. It has been shown that organic reaction mixtures containing 4 Å molecular sieves (Type 4A sodium aluminosilicates) are typically basic in nature, with measured pH of slurry solutions in the pH 9–11 range. For more information, see: (a) Davis, M. E. *Ind. Eng. Chem. Res.* **1991**, *30*, 1675 and references therein; (b) Herr, R. J.; Meckler, H.; Scuderi, Jr., F. *Org. Process Res. Dev.* **2000**, *4*, 43; (c) Sigma Aldrich Technical Information Bulletin AL-143: Mineral Adsorbents, Filter Agents, and Drying Agents (Accessed 1/14/13).
17. *General experimental procedure*: $Bi(OTf)_3$ (0.05 mmol) and 4 Å molecular sieves (200 mg) were placed in a small screw-cap scintillation vial equipped with a magnetic stir bar. Allylic halide (0.5 mmol) and dichloromethane (1 mL) were added and the mixture was stirred at room temperature for 16 h. The mixture was filtered through a pad of Celite, eluting with ethyl acetate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to afford analytically pure cyclized product. See Supplementary data for details concerning preparation of precursors.
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