

Azepines

A Catalytic Diastereoselective Formal [5+2] Cycloaddition Approach to Azepino[1,2-*a*]indoles: Putative Donor–Acceptor Cyclobutanes as Reactive Intermediates**

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Abstract: A catalytic formal [5+2] cycloaddition approach to the diastereoselective synthesis of azepino[1,2-*a*]indoles is reported. The reaction presumably proceeds through a Lewis acid catalyzed formal [2+2] cycloaddition of an alkene with an *N*-indolyl alkylidene β -amide ester to form a donor–acceptor cyclobutane intermediate, which subsequently undergoes an intramolecular ring-opening cyclization. Azepine products are formed in up to 92 % yield with high degrees of diastereoselectivity (up to 34:1 d.r.).

The azepino[1,2-*a*]indole skeleton (**1**) is a key structural element that appears in the core structures of an impressive number of naturally occurring indole alkaloids and pharmaceutically relevant compounds (Figure 1). For instance, correantine B (**2**) represents a larger group of indole alkaloids isolated from *Psychotria correae*.^[1] Akagerine (**3**) has demonstrated antiprotazoal properties and has been the target of

a number of synthetic endeavors.^[2] Similarly, cyclopropyl azepine **4** is a member of a small molecule library (>1000 compounds) developed by Bristol–Myers Squibb as Hepatitis C NS5B inhibitors,^[3] whereas compound **5** was studied as a promising prostaglandin D2 receptor agonist.^[4] Indolocarbazole **6** is a potent D1/CDK4 inhibitor and an antiproliferative agent in HCT-116 and NCI-460 cell lines.^[5] Other interesting azepino[1,2-*a*]indoles have also been shown to be competent melatonin receptor agonists^[6] and anti-parasitic agents.^[7]

Approaches to this framework have relied on olefin metatheses,^[8] hetero-[5+2] cycloadditions,^[9] radical cyclizations,^[10] or transition-metal-catalyzed intramolecular cyclization cascades.^[11] Unfortunately, these methods have limitations, which include high catalyst loadings, low functional group tolerance, and/or multiple steps to generate the necessary precursors. Thus, the development of a more generalized method to this core structure remains a formidable challenge for organic chemists.

Over the past several years, we have developed a variety of intramolecular ring-opening cyclizations of donor–acceptor (D–A) cyclopropanes^[12] and activated cyclopropanes^[13] as a means to access a range of diverse molecules. Inspired by our previous work, we envisioned a Lewis acid catalyzed approach involving intramolecular ring-opening cyclizations of D–A cyclobutanes to access the azepino[1,2-*a*]indole core (Scheme 1).

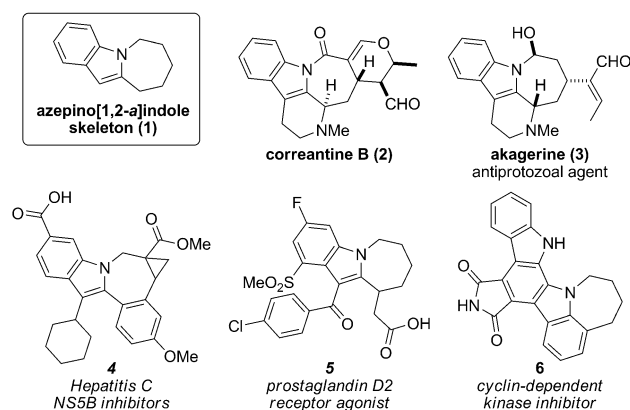
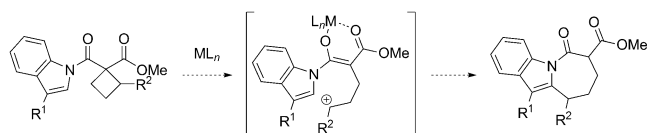


Figure 1. Examples of natural and unnatural bioactive azepino[1,2-*a*]indoles.



Scheme 1. Proposed intramolecular ring-opening cyclizations of D–A cyclobutanes.

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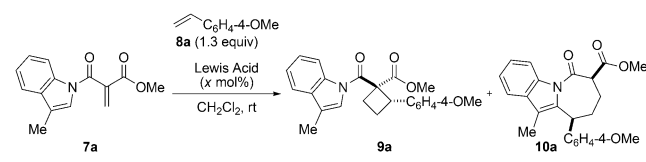
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Whereas D–A cyclopropanes have been extensively studied,^[14] D–A cyclobutanes have been underutilized in organic synthesis.^[15] Examples of using D–A cyclobutanes for ring-opening C–C bond-forming reactions beyond ring expansions are limited to a handful of reports. A seminal report by Shimada and co-workers in 1991 described formal [4+2] cycloadditions of D–A cyclobutanes with aldehydes and ketones.^[16] Almost twenty years passed before similar examples were reported by the groups of Johnson,^[17] Christie,^[18] Pagenkopf,^[19] and Waser.^[20] Over the past four years, Pagenkopf et al. have expanded the intermolecular reactivity of D–A cyclobutanes beyond carbonyl compounds to include

imines,^[21] nitrosoarenes,^[22] nitrones,^[23] and alkynes.^[24] Despite these important examples, we are unaware of any reports of D–A cyclobutanes undergoing intramolecular ring-forming reactions.^[25]

To explore such a transformation, we sought to prepare the desired D–A cyclobutanes using Lewis acid promoted formal [2+2] cycloadditions of alkylidene malonates with alkenes. In hopes of accessing the azepine core, we began our study using alkylidene **7a**^[26] and 4-methoxystyrene (**8a**) as the model substrates (Table 1).

Table 1: Optimization of the reaction conditions.^[a]

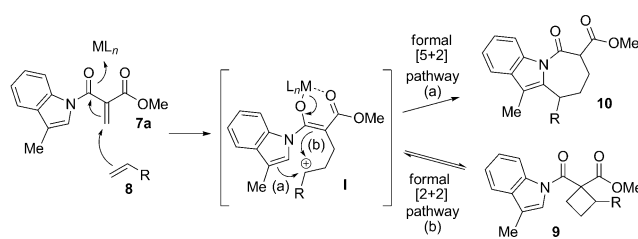


Entry	Lewis acid (mol %)	t [h]	Yield ^[b] [%]	9a / 10a ^[c]
1	ZnBr ₂ (100)	24	52	0:1
2	ZnBr ₂ (10)	24	62	1:1.3
3	Sc(OTf) ₃ (20)	1	72	0.1
4	Sc(OTf) ₃ (10)	2	78	0:1
5	Yb(OTf) ₃ (10)	7	44	1:1.3
6	Mg(OTf) ₂ (10)	48	25	0:1
7	La(OTf) ₃ (10)	7	25	1.6:1

[a] Reaction conditions: Lewis acid, **8a** (1.3 equiv), **7a** (1.0 equiv), CH₂Cl₂ (0.17 M), 22 °C. [b] Combined yield of **9a** and **10a** after column chromatography. [c] Product ratios determined from the yields of isolated products. See the Supporting Information for full details of the Lewis acid screening, including diastereomeric ratios.

We first chose to explore formation of the D–A cyclobutane using Roberts's ZnBr₂-promoted formal [2+2] cycloaddition approach (entry 1).^[27] When alkylidene **7a** and 4-methoxystyrene (**8a**) were treated with ZnBr₂ (100 mol %), the only product observed was azepino[1,2-*a*]indole **10a** in 52 % yield. At a ZnBr₂ loading of 10 mol %, a 1:1.3 mixture of cyclobutane **9a** and azepino[1,2-*a*]indole **10a** was obtained (entry 2). We then subjected **7a** and **8a** to the catalytic conditions developed by the groups of Johnson^[17a] (Sc(OTf)₃) and Pagenkopf^[19] (Yb(OTf)₃). Using Sc(OTf)₃ at loadings of 20 and 10 mol %, azepine **10a** was formed in 72 % and 78 % yield, respectively (entries 3 and 4). With 10 mol % of Yb(OTf)₃, a 1.3:1 mixture of azepine and cyclobutane was observed in 44 % combined yield (entry 5). It should be noted that whenever azepinoindole **10a** was formed, the *cis/trans* diastereomeric ratio (d.r.) was > 8:1. All other Lewis acids screened afforded no reaction or poor yields of **9a** and **10a** (entries 6 and 7). Therefore, 10 mol % of Sc(OTf)₃ proved to be optimal for the direct synthesis of azepino[1,2-*a*]indole **10a** (78 % yield, 33:1 d.r.).

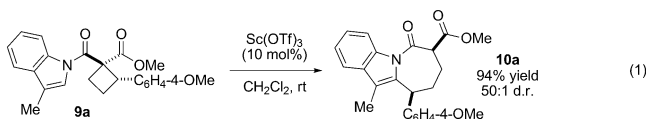
Given the observed reaction outcomes, our focus became the tandem formal [2+2] cycloaddition/ring-opening cyclization. In essence, the transformation is a formal [5+2] cycloaddition of alkylidene **7a** and alkene **8a**. Mechanistically, the reaction initially involves Lewis acid activation of the alkylidene followed by intermolecular attack of the alkene in a Michael addition to form the 1,4-dipolar intermediate **I**



Scheme 2. Proposed mechanism.

(Scheme 2). Intermediate **I** can either undergo a direct intramolecular Friedel–Crafts-type alkylation (pathway a: formal [5+2] pathway) to afford azepino[1,2-*a*]indole **10**, or a 4-(enol-*exo*)-*exo-trig* cyclization (pathway b: formal [2+2] cycloaddition pathway) to form cyclobutane **9**. Cyclobutane **9** can readily revert back to intermediate **I** depending on the Lewis acid catalyst. Given entropic considerations for seven-membered ring formation,^[28] it is plausible that the reaction proceeds via the cyclobutane first, followed by a rapid ring-opening cyclization to azepine **10**. However, at this stage, it is impossible to rule out the possibility of two parallel pathways.^[29]

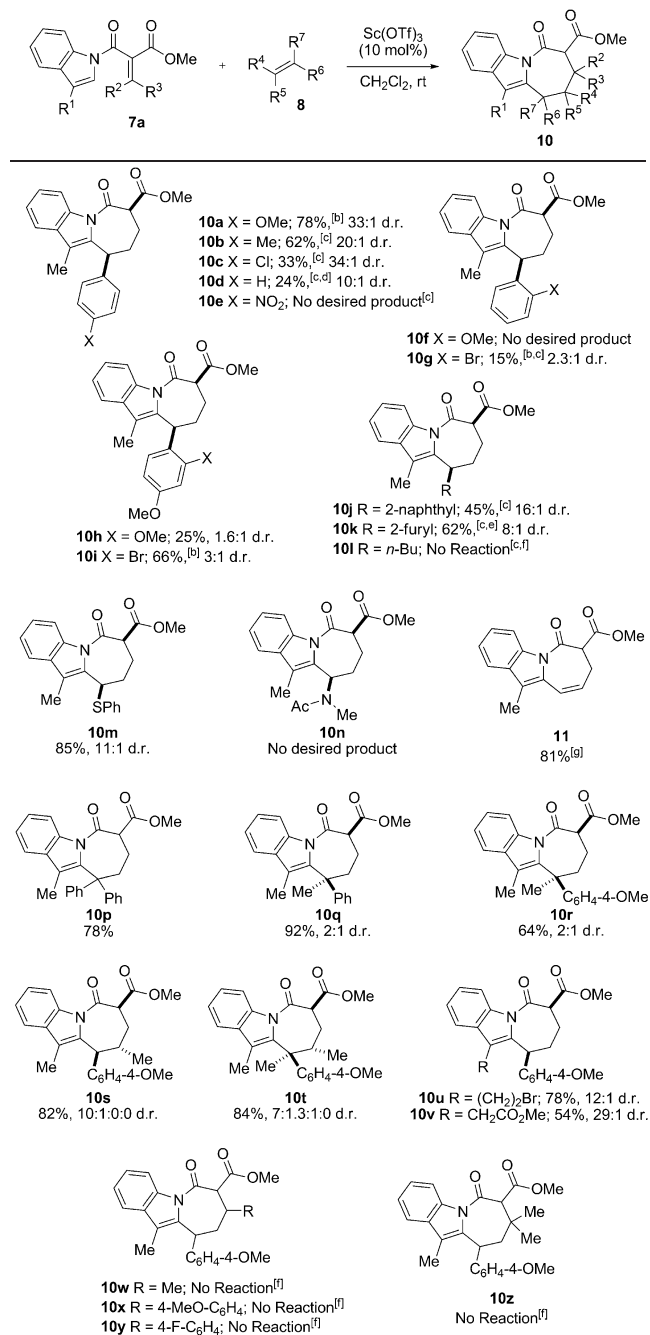
To support the hypothesis that **10** might be an intermediate in the reaction, cyclobutane **9a** was isolated and subjected to the standard reaction conditions [Eq. (1)]. To our delight, azepino[1,2-*a*]indole **10a** was obtained in 94 % yield with a *cis/trans* d.r. of 50:1 in under one hour.



The diastereoselectivity of the reaction presumably arises during the protonation step and not during formation of the C–C bond. The observed *cis* diastereoselectivity can be rationalized through an examination of the conformation of the Lewis acid–azepino[1,2-*a*]indole enolate complex (see the Supporting Information). The enolate complex is expected to adopt the flexible cycloheptenone twist-chair conformation,^[30] which forces a certain degree of non-planarity into the *N*-acyl indole moiety. Facial bias arises as the preference for pseudoaxial protonation gives rise to the observed *cis* product (kinetic product).^[31]

With a working method in hand, the scope, limitation, and stereochemical outcome of the formal [5+2] cycloaddition reaction were examined by employing different substituted alkenes and *N*-indolyl alkylidene β-amide esters (Table 2). For the optimized reaction with 4-methoxystyrene, azepino[1,2-*a*]indole **10a** was formed in 78 % yield with 33:1 d.r. (*cis/trans*). Styrenes with weakly electron-donating substituents in the *para* position gave the corresponding azepines in reduced yield (**10b** and **10c**), albeit with high d.r. (> 20:1). Product **10d** (from styrene) was formed with a somewhat reduced d.r. (10:1), whereas the desired azepine (**10e**) was not produced with electron-deficient 4-nitrostyrene. Surprisingly, in stark

Table 2: Catalytic formal [5+2] cycloaddition of alkylidenes **7** and alkenes **8**.^[a]



[a] Reaction conditions: Sc(OTf)₃ (10 mol %), **8** (5.0 equiv), and **7a** (1.0 equiv) in CH₂Cl₂ (0.17 M) at 22 °C. Yields of isolated products after column chromatography are given. Diastereomeric ratios (d.r.) were determined by ¹H NMR spectroscopy of the crude reaction mixture.
 [b] Reaction run with alkene (1.3 equiv). [c] Reaction performed at reflux.
 [d] Reaction performed with Sc(OTf)₃ (20 mol %). [e] Reaction performed with Yb(OTf)₃ (5 mol %). [f] Only starting materials recovered.
 [g] From cyclobutane **9o**.

contrast to 4-methoxystyrene, no azepine product was generated with 2-methoxystyrene (**10f** not formed). Instead, only degradation/polymerization products were detected. The observed side reactions are likely due to undesired steric repulsion between the *ortho* substituent and the indole methyl

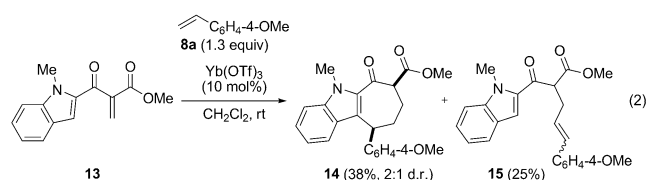
group, which prevents ring closure to form the azepine ring. Reduced yields and/or diastereoselectivities were similarly obtained when other *ortho*-substituted styrenes were employed (**10g–10i**).

Azepino[1,2-*a*]indole **10j** (derived from 2-vinyl naphthalene) was generated in 45 % yield with 16:1 d.r. when the reaction mixture was heated at reflux. In the presence of Sc(OTf)₃, 2-vinylfuran degraded (**10k** not formed). However, with Yb(OTf)₃ as the catalyst, furyl azepine **10k** was isolated in good yield and with good diastereoselectivity (62 %, 8:1 d.r.). In contrast to the reactions with aryl alkenes, no reactivity was observed with an alkyl alkene (1-hexene). Next, alkenes bearing heteroatoms were studied. Vinyl sulfides were readily tolerated. For example, phenyl vinyl sulfide afforded **10m** in 85 % yield and 11:1 d.r. However, no azepine product (**10n**) was obtained when *N*-methyl-*N*-vinylacetamide was employed.^[32] Whereas the Michael addition of the enamide to the alkylidene readily occurred, the subsequent intramolecular Mannich reaction did not.^[33] On the other hand, when ethyl vinyl ether was subjected to 10 mol % Yb(OTf)₃, only cyclobutane **9o** was isolated (see the Supporting Information). Subjecting isolated cyclobutane **9o** to the reaction conditions gave 7,8-dihydro-6*H*-azepino[1,2-*a*]indole **11** in 81 % yield. The unsaturation arises from the Lewis acid mediated elimination of EtOH after formation of the seven-membered ring.^[34]

1,1-Disubstituted alkenes readily gave the desired products as long as one of the substituents was aromatic. For instance, the reaction of **7a** with 1,1-diphenylethylene afforded azepine **10p** in 78 % yield. When α -methylstyrene was employed, azepino[1,2-*a*]indole **10q** was produced in 92 % yield with only 2:1 d.r. This reduced selectivity can be rationalized by the relatively small difference in steric influence (*A* values) for the methyl group versus the phenyl group (1.8 vs 2.8 kcal mol⁻¹).^[35] A similar diastereomeric ratio was observed for the product (**10r**) from α -methyl-4-methoxystyrene. β -Methyl-4-methoxystyrene smoothly gave its azepino[1,2-*a*]indole product **10s** (82 %, 10:1:0:0 d.r.). Finally, when a trisubstituted alkene was used, the resulting azepine **10t** was obtained in 84 % yield with a d.r. of 7:1.3:1:0.

Finally, changes to the substituent at the 3-position of the indole moiety were investigated. Alkylidenes derived from 3-(2-bromoethyl)indole and indole acetic acid methyl ester readily reacted with 4-methoxystyrene to give the expected azepines **10u** and **10v** in 78 % yield and 54 % yield, respectively. However, when alkyl or aryl substituents were placed on the alkylidene, no reactivity was observed (**10w–10z** not formed), and the alkylidenes were fully recovered. The lack of reactivity presumably originates from undesired steric interactions between the ester group and the alkylidene substituent that force the enone into the unreactive *s-cis* conformation.^[36]

Given the importance of the indole moiety to the pharmaceutical and chemical industries,^[37] the feasibility of forming indole-fused cycloheptanones was explored by using the C-acylated indolyl alkylidene β -ketoester **13** under the reaction conditions [Eq. (2)]. When alkylidene **13** was reacted with 4-methoxystyrene in the presence of Sc(OTf)₃ (10 mol %), no desired products were obtained. In contrast,



when $\text{Yb}(\text{OTf})_3$ (10 mol %) was employed, hexahydrocyclohepta[b]indole **14** was obtained in 38 % yield (2:1 d.r.) along with olefin **15** as the major side product (25 %). Owing to the reduced nucleophilicity at the C3 position of the indole in the acyclic intermediate, E1 elimination competes with ring closure to form **15**.

In summary, we have developed a diastereoselective Lewis acid catalyzed approach to azepino[1,2-*a*]indoles that involves a formal [2+2] cycloaddition followed by a cyclobutane ring-opening cyclization. This tandem transformation represents a formal [5+2] cycloaddition. Various alkenes are compatible with this method, including aromatic alkenes and vinyl sulfides. Azepino[1,2-*a*]indoles are formed in up to 92 % yield in modest to high diastereomeric ratios (up to 34:1 d.r.). We have also demonstrated the first examples of Lewis acid catalyzed intramolecular ring-opening cyclizations of D-A cyclobutanes. To date, these approaches represent the most efficient routes to a functionalized azepino[1,2-*a*]indole core. A deeper examination of the mechanism is currently underway and will be reported in due course. We will also explore intramolecular reactions and the formation of other useful fused cycloheptanones and develop an asymmetric variant of this transformation. Finally, reactions with different enamides and other vinyl amines will be studied in greater detail.

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