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Calcium-Catalyzed Formal [5 + 2] Cycloadditions of Alkylidene β-Ketoesters with Olefins: Chemodivergent Synthesis of Highly Functionalized Cyclohepta[b]indole Derivatives

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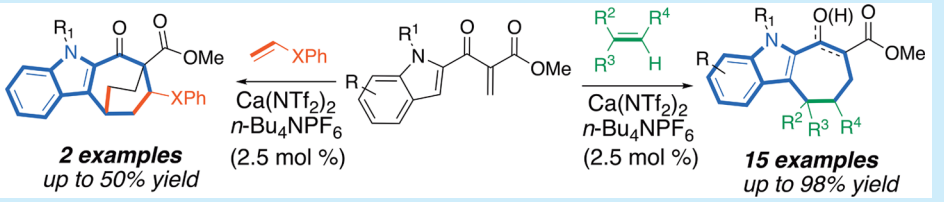
Supporting Information



ABSTRACT: The calcium-catalyzed, formal [5 + 2] cycloaddition of indolyl alkylidene β-ketoesters with mono- and disubstituted aryl olefins to form cyclohepta[b]indole derivatives has been established. Unanticipated chemodivergence with phenyl vinyl sulfide/ether revealed a double [5 + 2] cycloaddition cascade providing ethano-bridged cyclohepta[b]indoles. Overall, the method's highlights include: (1) use of a green, calcium-based catalyst (2.5 mol % loading); (2) reaction times under 1 h; (3) mild reaction conditions; (4) substrate-derived chemodivergence; (5) functional group tolerance; and (6) examples of derivatization.

The cyclohepta[b]indole framework (**1**)[1] is a common core of a number of bioactive naturally occurring indole alkaloids such as actinophyllic acid (fibrinolysis inhibitor),[2] exotine B (inhibitor of liposaccharide-induced nitric oxide production),[3] and the anticholinergic agent, methuenine[4] (Figure 1). This 6,5,7-tricyclic indole-fused seven-membered

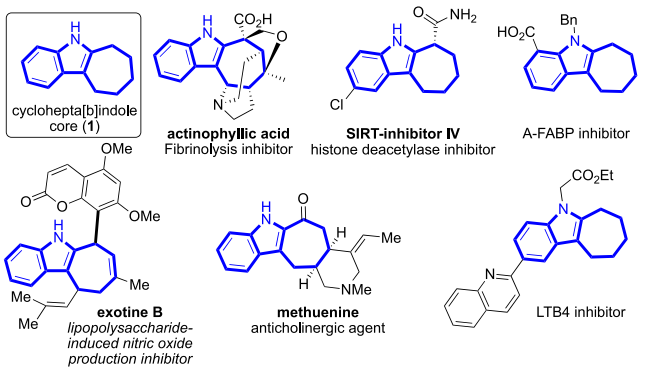


Figure 1. Representative cyclohepta[b]indole-containing compounds.

ring system also represents a privileged scaffold in the pharmaceutical industry. It is present in a series of synthesized molecular targets exhibiting inhibitory biological activity against histone deacetylase SIRT1,[5] adipocyte fatty-acid binding protein,[6] and leukotriene B4 production.[7]

Owing to the promising biological profiles of cyclohepta[b]indole-containing molecules, tremendous interest from both medicinal and synthetic organic chemists has resulted in numerous patents being issued within the past decade and a number of synthetic approaches to the scaffold being reported.[8] However, each method has its own limitations including lack of functional group tolerance, harsh reaction conditions, low atom economy, or poor scalability. This has led to general difficulty in preparing cyclohepta[b]indoles that are differentially functionalized on the seven-membered ring. For example, historically, the Fischer indolization was the primary method in preparing the motif.[9] However, due to requirement of a prefunctionalized cycloheptyl ring, the method is highly limited in producing highly functionalized, unsymmetrical cyclohepta[b]indoles. Thus, alternative approaches to the framework have been targeted, which include metal-mediated intramolecular cyclization cascades,[10] olefin metathesis,[11] [3,3]-sigmatropic rearrangements with divinylcyclopropanes,[5,12] [4 + 3]-cycloadditions,[13] and [5 + 2]-cycloadditions.[14] Of the previous methods mentioned, the cycloaddition reactions have proven to be the most efficient and atom-economical approaches to the cyclohepta[b]indole as they construct the seven-membered ring in a single step with simultaneous or nearly simultaneous formation of two C−C bonds in a regio- and/or diastereoselective manner. Previously reported [4 + 3] cycloaddition reactions utilized *in situ* generated highly reactive intermediates such as indolyl carbocations,[13a,d,e,h] oxyallyl cations,[13f] and metal carbe-

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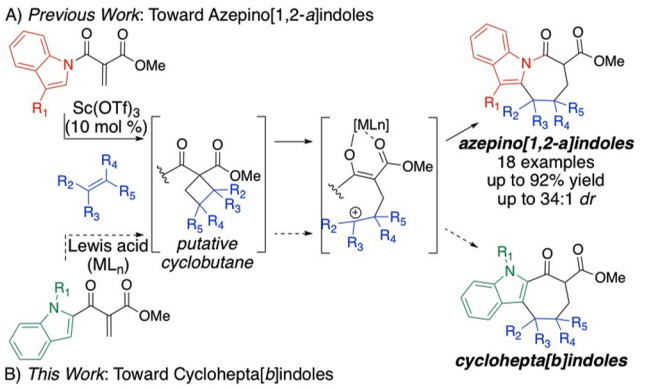
nes.[13b,c,g] While [4 + 3] cycloaddition approaches toward cyclohepta[*b*]indoles are found abundantly throughout the literature, there are currently only two known examples of [5 + 2] cycloaddition reactions toward this privileged motif. The first method was reported by Li et al.[14b] and furnished oxacyclohepta[*b*]indoles via an intramolecular dearomative indole [5 + 2] cycloaddition using an oxidopyrylium ylide. More recently, Nishida et al.[14a] developed an intermolecular [5 + 2] cycloaddition of alkynes and 2-((1*H*-indol-2-yl)methyl)-acrylates where the indium(III) catalyst acts as both a π-Lewis acid and σ-Lewis acid to activate both the alkyne and enoate moiety. Unfortunately, as stated above, the highlighted cycloaddition methods are limited by high catalyst loading, low functional group tolerance, and/or a multistep synthesis necessary to generate the cycloaddition precursor/reactive intermediate, which results in limited functionality on the cycloheptanoid ring. Thus, the development of a versatile method toward highly functionalized cyclohepta[*b*]indoles still remains a worthwhile endeavor.

Toward this end, we sought an approach to the cyclohepta-[*b*]indole core inspired by our report on the formal [5 + 2] cycloaddition of *N*-indolyl alkylidene β-amide esters with substituted olefins and to form azepino[1,2-*a*]indoles (Scheme 1).[15] The Lewis-acid-catalyzed reaction proceeds through a

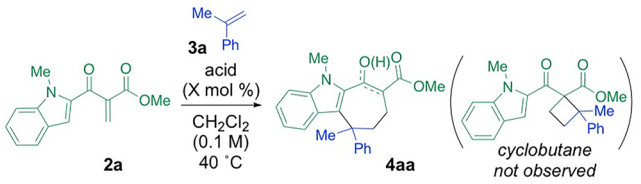
Scheme 1. Formal [5 + 2] Cycloadditions of Indolyl Alkylidene β-Ketoesters and Olefins



putative cyclobutane intermediate (via formal [2 + 2] cycloaddition) that undergoes Friedel–Crafts-type ring-opening cyclization to form the azepinoindole. Choice of the Lewis acid catalyst determines the extent of the [5 + 2] vs [2 + 2] pathways. Thus, we envisioned that, by employing the analogous *C*-acylated indolyl alkylidene β-ketoester, the cyclohepta[*b*]indole framework should be similarly accessible.

Alkylidene **2a**, which is readily accessible in two steps from commercially available 1-methylindole-2-carboxylic acid, was selected as the model substrate (Table 1). To probe the formal [5 + 2] reaction,[15] α-methylstyrene (**3a**) was chosen as the reactive partner. Given its effectiveness in the azepinoindole system, 10 mol % of $Sc(OTf)_3$ was initially screened, providing 51% yield of **4aa** as a complex keto–enol mixture when the reaction was performed at room temperature in CH_2Cl_2 (entry 1). An improved yield (65%) was obtained when the reaction was conducted at reflux (entry 2). Decreasing the catalyst loadings to 5 mol % and 2.5 mol % afforded the desired product **4aa** with the same 66% yield (entries 3 and 4). At this point, other Lewis acids were screened (at 2.5 mol % loading) in hopes of both improving reaction yields and identifying any

Table 1. Catalyst Screening[a]



entry	acid (mol %)	time (h)	yield (%)[b]
1[c]	$Sc(OTf)_3$ (10)	1.0	51
2	$Sc(OTf)_3$ (10)	0.5	65
3	$Sc(OTf)_3$ (5)	1.0	66
4	$Sc(OTf)_3$ (2.5)	1.0	66
5	$Ga(OTf)_3$ (2.5)	1.0	67
6	$Zn(OTf)_2$ (2.5)	0.5	44
7	$Yb(OTf)_3$ (2.5)	1.0	51
8	$Mg(OTf)_2$ (2.5)	1.5	0[d]
9	$Al(OTf)_3$ (2.5)	1.0	73
10	$Hf(OTf)_4$ (2.5)	0.5	73
11	**$Ca(NTf_2)_2$ (2.5); *n*-Bu_4NPF_6 (2.5)**	**0.5**	**98**
12[c]	$Ca(NTf_2)_2$ (2.5); *n*-Bu_4NPF_6 (2.5)	0.5	73
13	$Ca(NTf_2)_2$ (2.5)	24.0	0[d]
14	*n*-Bu_4NPF_6 (2.5)	24.0	0[e]
15	$HNTf_2$ (2.5)	1.5	64

[a]Reaction performed with alkylidene **2a**, α-methylstyrene (**3a**, 5 equiv), and indicated acid catalyst in CH_2Cl_2 (0.1 M) at 40 °C. [b]Isolated yield of **4aa** after column chromatography. [c]Reaction performed at room temperature. [d]No desired products obtained. [e]No reaction.

selective conditions for cyclobutane formation. $Ga(OTf)_3$ led to the cyclohepta[*b*]indole product mixture in 67% yield without any cyclobutane formation (entry 5). $Zn(OTf)_2$ similarly generated a 44% yield of only cyclohepta[*b*]indole **4aa** (entry 6). $Yb(OTf)_3$, which selectively afforded cyclobutane in our previous report, gave only cyclohepta[*b*]indole in 51% yield (entries 6 and 7). No desired products were obtained with $Mg(OTf)_2$ (entry 8). Both $Al(OTf)_3$ and $Hf(OTf)_4$ raised the cyclohepta[*b*]indole product yield to 73% (entries 9 and 10). Employed due its success in our previous intramolecular cyclizations, the Niggemann's Lewis acidic calcium complex[16] ($Ca(NTf_2)_2$ with *n*-Bu_4NPF_6 as an additive) produced the best yield of cyclohepta[*b*]indole **4aa** at 98% (entry 11). Consistent with the observed results with $Sc(OTf)_3$, reduced yields were obtained upon performing the calcium reaction at room temperature (entry 12). It is important to note that the cyclobutane was never detected under any of the reaction conditions, which is in sharp contrast with the azepino system.[15]

To ensure that the catalysis is due to the calcium–additive complex and not from its individual components, a series of control reactions were conducted. Performing the reaction without the additive, *n*-Bu_4NPF_6, afforded no desired product (entry 13). In contrast, while the reaction did not proceed to any appreciable degree without $Ca(NTf)_2$ present (entry 14), 64% yield of the desired product was obtained with $HNTf_2$ as the catalyst. Given this result, a synergistic Lewis and Brønsted acid effect between the formed calcium complex and $HNTf_2$ cannot be ruled out. Further efforts in optimizing temperature, solvent, and concentration led to no improvements in yield.[18] Thus, the optimized reaction conditions for the above transformation were 2.5 mol % of $Ca(NTf_2)_2$ and 2.5 mol % of *n*-Bu_4NPF_6 in CH_2Cl_2 (0.1M) with 5.0 equiv of alkene.

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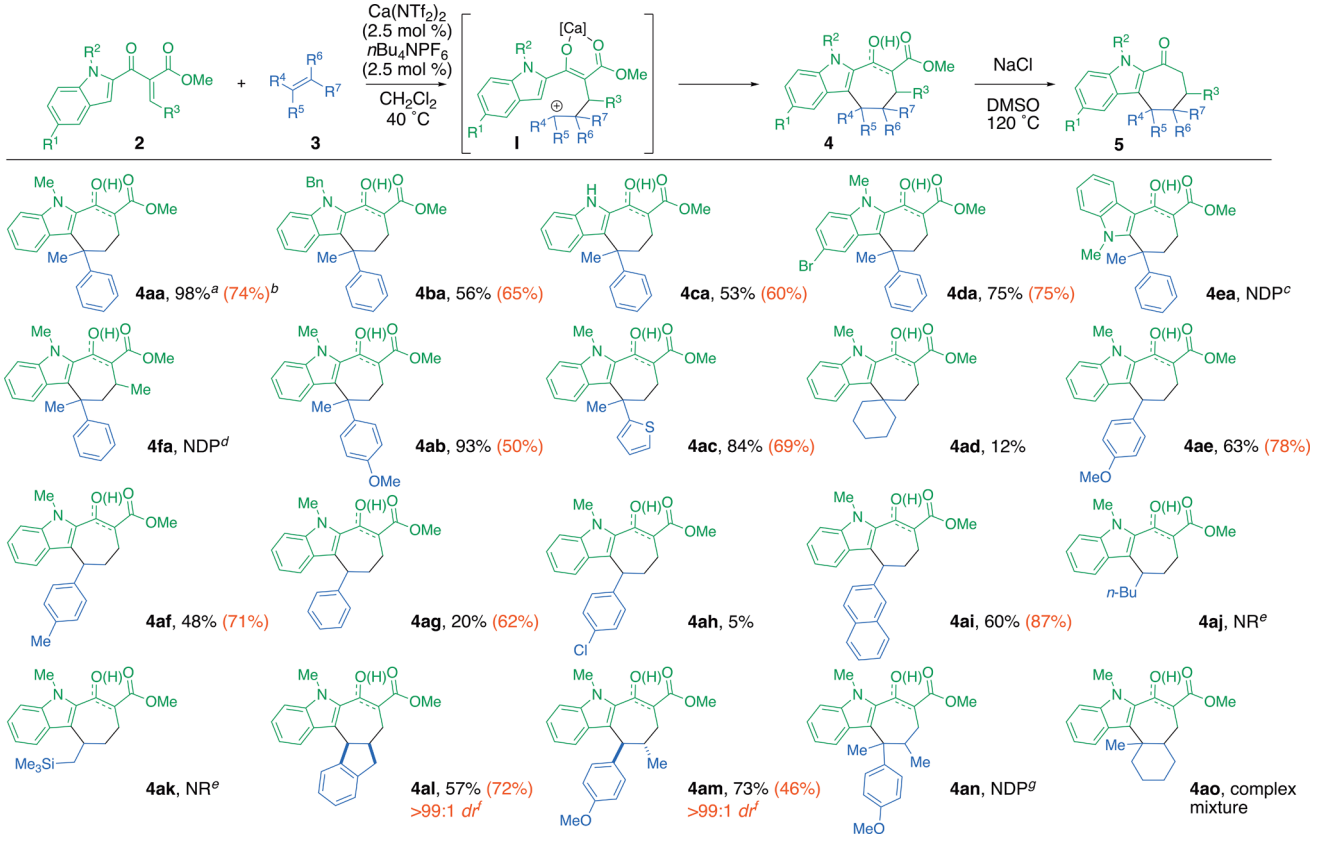
Scheme 2. Exploration of Reaction Scope



[a]Numbers represent isolated yields of **4** following column chromatography. [b]Numbers in parentheses are isolated yields of **5** following Krapcho decarbalkoxylation. [c]No desired product formed due to extensive degradation of alkylidene. [d]No desired product formed due to the formation of Nazarov cyclization byproduct. [e]No reaction. Only starting materials recovered. [f]Diastereomeric ratio determined by crude ^{1}H NMR of the Krapcho product. [g]No desired product formed due to alkene degradation.

Given that the [5 + 2] cycloaddition transformation resulted in the formation of a complex keto−enol mixture of the cyclohepta[*b*]indole product **4aa**, Krapcho decarbalkoxylation[17] was employed to simplify NMR analysis and validate product formation (Scheme 2). Treatment of **4aa** with NaCl in wet DMSO at 150 °C afforded ketone **5aa** in 74% yield.

With the promising results from the model system, the cycloaddition study was expanded to explore the substrate scope and general limitations (Scheme 2). First, changes to the indole moiety were somewhat tolerated. Both the *N*-benzyl and *N*-H (unprotected) alkylidenes (**2b** and **2c**) gave their cycloaddition products **4ba** and **4ca** with α-methylstyrene (**3a**) in 56% and 53% yield, respectively. Similarly, the 5-bromoindolyl alkylidene **2d** provided the cyclohepta[*b*]indole **4da** in 75% yield. To our dismay, no products (**4ea** or **4fa**) were obtained when α-methylstyrene was reacted with either the 3-acyl indolyl alkylidene **2e** (only degradation observed) or the methyl-substituted alkylidene **2f** (only competing Nazarov cyclization[18,19] product formed).

Next, other 1,1-disubstituted olefins were employed. As with α-methylstyrene, 4-methoxy-α-methylstyrene (**3b**) and 2-(prop-1-en-2-yl)thiophene (**3c**) each gave their respective cycloaddition products **4ab** and **4ac** in 93% and 84% yield. Methylene cyclohexane **3d**, a 1,1-dialkyl olefin, also afforded the expected cycloheptyl product **4ad** in 12% yield. The low yield is likely a result of the 1,1-dialkyl olefin being a much weaker nucleophile when compared to the α-substituted styrenes.

Monosubstituted olefins were subsequently examined. Electron-rich styrenes, such as **3e** (*p*-methoxy substituent) and **3f** (*p*-methyl substitutent), provided their respective products **4ae** and **4af** in 63% and 48% yield. While styrene (**3g**) gave its product **4ag** in 20% yield, only 5% yield of product **4ah** could be isolated with the more electron-poor substrate, *p*-chlorostyrene **3h**. 2-Vinylnaphthalene **3i** generated 60% of the cycloaddition product **4ai**. In contrast, when 1-hexene (**3j**, unactivated) or TMS allylsilane (**3k**, activated) was employed, no reaction was detected, and only starting materials were recovered.

1,2-Disubstituted olefins were then evaluated. Indene **3l** provided cycloaddition product **4al** in 57% yield, while *p*-methoxy-β-methylstyrene **3m** afforded cyclohelpta[*b*]indole **4am** in 71% yield. When **4al** and **4am** were subjected to Krapcho conditions, only one diastereomer of **5** was isolated in each case. Conversely, 1,1,2-trisubstituted olefins (**3n** and **3o**) proved untenable as complex mixtures were obtained or olefin polymerization/degradation (likely due to the presence of $HNTf_2$) was observed under the reaction conditions.

Interestingly, when phenyl vinyl sulfide (**3p**) was reacted with alkylidene **2a**, the anticipated cyclohepta[*b*]indole product **4ap** was not observed (Scheme 3). Instead, the bicyclic cyclohepta[*b*]indole framework **6ap** was isolated in 50% yield as a single diastereomer and confirmed by X-ray

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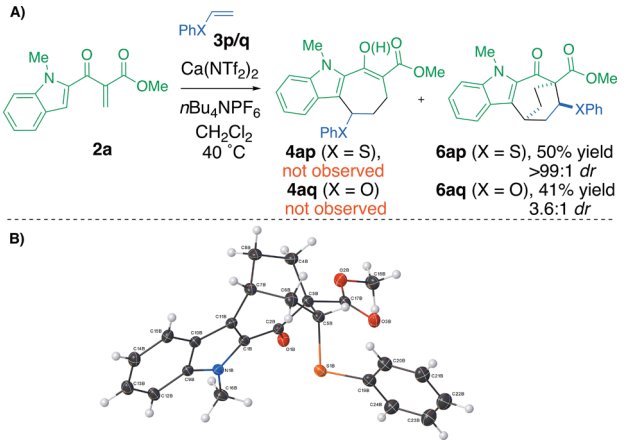
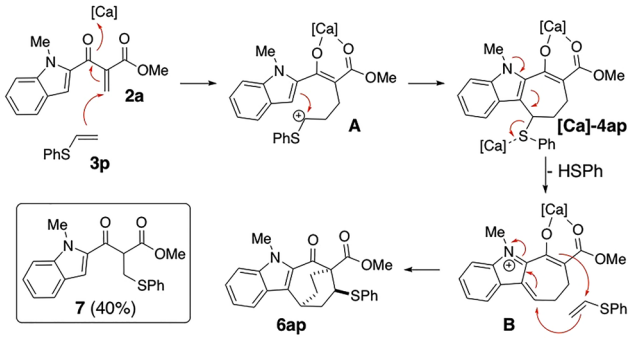
Scheme 3. (A) Unexpected Bicyclic Byproducts with Phenyl Vinyl Sulfide and Ether and (B) Crystal Structure of the Sulfide 6ap Drawn at the 50% Probability Level



crystallography. **6ap** contains an indole ring fused to a bicyclo[3.2.2]nonene moiety and represents an unprecedented cyclohepta[*b*]indole framework. A similar bicyclic product **6aq** was formed with phenyl vinyl ether **3q**, albeit with lower yield (41%) and diastereoselectivity (3.6:1 dr). Neither cyclohepta[*b*]indole product was obtained with cyclic/acyclic alkyl enol ethers or enamides.[18] This lack of reactivity is presumably due to the presence of $HNTf_2$, which appears to catalyze polymerization of the alkyl enol ethers and hydrolysis of the enamides. In comparison, **3p** and **3q** are less susceptible to acid catalysis and, thus, are amenable to the reaction conditions.

The bicyclic cyclohepta[*b*]indole derivative **6ap** is presumed to form through a cascade sequence that starts with the formation of the expected formal [5 + 2] cycloaddition product **4ap** (Scheme 4). Lewis acid activation of the phenyl

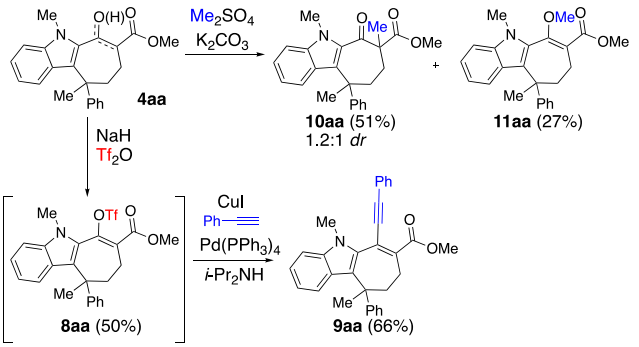
Scheme 4. Proposed Mechanism for Cascade Formation of Bicyclic Cyclohepta[*b*]indole 6ap



sulfide is assumed to facilitate C−X bond cleavage to provide the cationic, resonance-stabilized divinyl iminium intermediate **B** and PhS^-. *In situ* generation of PhS^- is supported by the formation of **7**,[20] the Michael addition product of phenyl sulfide, and the starting alkylidene **2a**. Finally, a subsequent [5 + 2] cycloaddition of intermediate **B** with another molecule of phenyl vinyl sulfide affords the observed bicyclic product **6ap**. This transformation is particularly interesting as, to the best of our knowledge, [5 + 2] cycloadditions involving divinyl iminium intermediates have not been previously reported in the literature.

Beyond decarbalkoxylation, the keto−enol mixtures of the cyclohepta[*b*]indole products can be readily derivatized (Scheme 5). For example, treatment of **4aa** with NaH and

Scheme 5. Facile Derivatization



Tf_2O afforded the corresponding enol triflate **8aa** in 50% yield. To highlight the versatility of this intermediate, **8aa** was then subjected to Pd-catalyzed Sonogashira coupling[21] with phenylacetylene to provide enyne **9aa** in 66% yield. Similarly, methylation of cyclohepta[*b*]indole **4aa** with K_2CO_3 and Me_2SO_4 resulted in 51% of the *C*-methylated product **10aa** (as a 1.2:1 diastereomeric mixture) and 27% of the *O*-methylated product **11aa**.

In summary, we have developed an efficient approach to highly functionalized cyclohepta[*b*]indoles. Using a low loading (2.5 mol %) of a green calcium-based catalyst, readily accessible olefins and *C*-acylated indolyl *α*-alkylidene *β*-ketoesters undergo formal [5 + 2] cycloadditions in <1 h providing substituted cycloheptyl rings. Competing cyclobutane formation ([2 + 2] cycloaddition) is not observed, whereas Nazarov cyclization is only observed (no [5 + 2]) with substituted alkylidenes. Various 2-acyl indoles are tolerated, thus allowing for tunable substitution about the cyclohepta[*b*]indole framework. Mono- and disubstituted aryl alkenes are particularly compatible with the method and give products in up to 98% yield. Interestingly, when either phenyl vinyl sulfide or ether are employed, an unanticipated chemodivergence was observed affording ethano-bridged cyclohepta[*b*]indoles in up to 50% yield. These products presumably form from the expected [5 + 2] cycloaddition product following PhXH elimination to form a divinyl iminium intermediate, which undergoes an unprecedented [5 + 2] cycloaddition. A deeper examination of this double [5 + 2] cycloaddition pathway is currently underway and will be reported in due course. Finally, examples of cyclohepta[*b*]indole product derivatization highlight the general practicality of this method.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02498.

Experimental procedures and spectral and analytical data for all new compounds (PDF)

Accession Codes

CCDC 1941328 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing

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All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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