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Tandem Gold-Catalyzed Dehydrative Cyclization/Diels–Alder Reactions: Facile Access to Indolocarbazole Alkaloids

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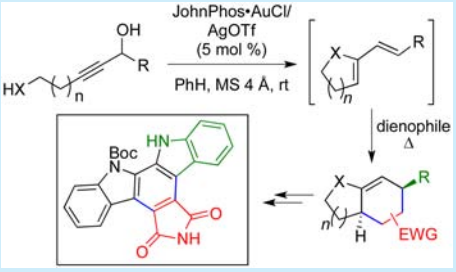
Supporting Information

ABSTRACT: A gold-catalyzed synthesis of cyclic 2-oxodienes from readily prepared propargyl alcohols and the subsequent Diels–Alder reaction are reported. The dehydrative cyclization reactions proceeded smoothly, and the dienes formed in situ were demonstrated to undergo cycloaddition with a variety of dienophiles. This method offers a new strategy for the synthesis of indolocarbazole alkaloids, whereby the convergent synthetic design allows for differentiation between the indole nitrogens.

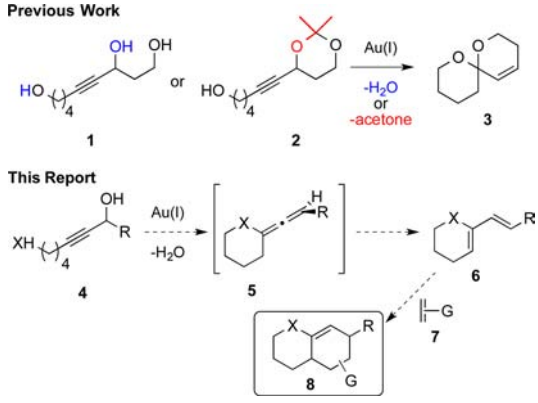


1,3-Dienes are an important building block for organic synthesis, finding use in a wide variety of reactions such as polymerization reactions,[1] olefin addition reactions,[2] and metathesis reactions[3] to name a few.[4] Of this highly diverse set of synthons, electron-rich dienes have proven to be particularly valuable, with one of the most well-known being the venerable Danishefsky's diene for Diels–Alder reactions.[5] While this 1,3-dioxygen-substituted reagent has found extensive use in natural product synthesis,[6] the analogous 2-alkoxy-substituted dienes[7] are much less frequently encountered. Despite the reduced occurrence, some extremely powerful and elegant applications that take advantage of this functionality have been reported. For instance, Barriault and co-workers employed a Diels–Alder/Claisen sequence in their approaches to penostatin F[8] and the tricyclic core of vinigrol.[9] Nicolaou utilized a 2-alkoxy-1,3-diene to introduce further oxygenation in the synthesis of brevetoxin A,[10] and Corey prepared analogues of the wood fragrances, georyone and arborone, via a Diels–Alder/olefin isomerization.[11]

In the aforementioned examples, preparation of a 2-vinyl-dihydropyran or alternative 2-vinyl oxygen heterocycle is required. Several groups have developed methodologies to arrive at these useful intermediates, and the synthetic protocols reported typically focus on enol ethers, lactones, or sugar derivatives as starting materials with the introduction of unsaturation by cross-coupling reactions,[12] Wittig olefination,[13] or a vinyl organometallic addition/dehydration sequence.[14] In light of the utility of these compounds and the sensitive nature of the enol ether functional group, we postulated that a mild, catalytic method to generate 2-oxodienes from readily available starting materials would be highly advantageous when coupled with the Diels–Alder reaction. Herein, we report a tandem Au-catalyzed diene synthesis/Diels–Alder reaction sequence and its application to the synthesis of indolocarbazole alkaloids.

As part of a program aimed at developing new dehydrative transformations of unsaturated alcohols, we previously reported the gold-catalyzed cyclization of monopropargylic triols **1**[15] and acetonides **2**[16] to form unsaturated spiroketals **3** (Scheme 1). Mechanistic investigations[15] suggested the intermediacy of allene **5**, and diene **6** was observed in a control experiment.[17] Considering the mild conditions employed and that water is the only byproduct of the reaction, we sought to investigate the possibility of utilizing this pathway for the synthesis of the requisite dienes **6** and then employing them in subsequent Diels–Alder reactions. Successful implementation of this strategy would constitute a facile and efficient approach to the Diels–Alder adducts **8**, which have been demonstrated to be valuable synthetic intermediates.[8−11]

Scheme 1. Au-Catalyzed Diene Synthesis



To examine the feasibility of this idea, substrates for the reaction were prepared in a straightforward manner from commercially available alkynols.[18] Several catalysts and conditions were screened using diol **9** as a prototypical substrate (Table 1). The best results were achieved with the JohnPhos·

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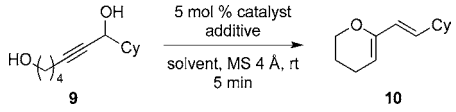
Table 1. Optimization Studies of Diene Formation

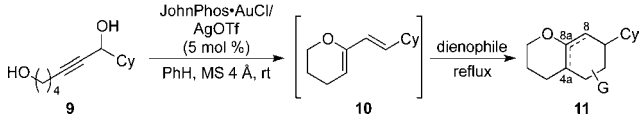


entry	catalyst	additive	solvent	yield (%)
1	JohnPhos·AuCl	AgOTf	THF	41
2	JohnPhos·AuCl	AgOTf	MeCN	28
3	JohnPhos·AuCl	AgOTf	PhH	81
4	PPh_3AuCl	AgOTf	PhH	73
5	$AuCl_3$		PhH	55

AuCl/AgOTf catalytic system and benzene as solvent (entry 3), whereby diene **10** was isolated in 81% yield after a 5 min reaction time. Interestingly, with all conditions screened, a rapid reaction to produce the diene was observed, demonstrating the high propensity of propargyl alcohols toward Au-catalyzed dehydrative transformations.

With the reaction conditions established for efficient diene formation, in situ trapping of this reactive compound by Diels–Alder cycloaddition was next explored. Initial experiments were performed using diol **9** with 5 mol % of JohnPhos·AuCl/AgOTf in the presence of a dienophile in benzene at ambient temperature before increasing the temperature to effect cycloaddition. Electron-deficient dienophiles were expected to give the best results based on reports by Guiliano,[13] Mori,[19] and others.[20] As seen in Table 2, with maleic anhydride and *N*-

Table 2. Optimization Studies of the One-Pot Reaction

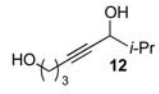
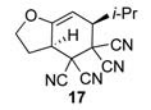
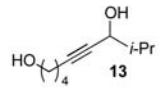
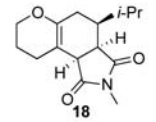
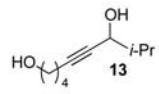
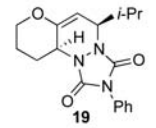
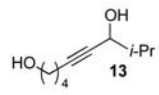
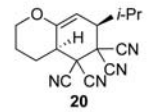
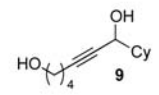
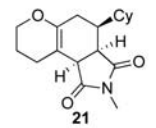
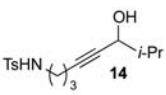
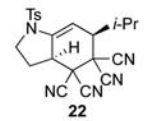
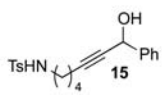
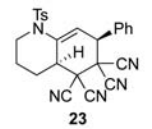
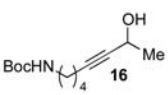
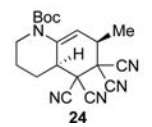


entry	dienophile	time (h)	yield (%)
1	maleic anhydride	48	46
2	*N*-methylmaleimide	48	82
3	dimethyl acetylenedicarboxylate	24	no rxn

methylmaleimide (NMM) (entries 1 and 2), the reaction sequence did indeed furnish the cycloadduct; however, it was found that the double bond had isomerized to the tetrasubstituted $\Delta_{4a,8a}$ olefin instead of the predicted $\Delta_{8,8a}$ position shown in **11**.[21] Remarkably, the two-step one-pot sequence with NMM provided the product in 82% yield (Table 2, entry 2), which is essentially identical to the isolated yield of the diene above (Table 1, entry 3).

Attention was next turned to examining the reaction scope with oxygen- and nitrogen-bearing substrates as well as different dienophiles. As seen in Table 3, both five- and six-membered ring dienes were readily formed with both oxygen (e.g., entries 1 and 4) and nitrogen (e.g., entries 6 and 7) nucleophiles, providing the Diels–Alder adducts in good to excellent yield and diastereoselectivity. Dienophiles such as NMM, tetracyanoethylene (TCNE), and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) performed well under the reaction conditions. Interestingly, as in Table 2, cycloadducts resulting from reactions with maleimides all underwent isomerization of the double bond to form the more thermodynamically stable tetrasubstituted olefin. It is unclear why this is consistently observed with NMM but no isomerization occurs with other dienophiles.

Table 3. Substrate Scope[a]

entry	alkyne	dienophile	product	yield (%), dr
1		TCNE		78 >25:1
2		NMM		79 >25:1
3		PTAD		54 >25:1
4		TCNE		91 >25:1
5		NMM		82 >25:1
6		TCNE		75 >25:1
7		TCNE		69 3:2
8		TCNE		80 4:1

[a]Reaction conditions: 2 mol % of JohnPhos·AuCl/AgOTf, benzene, 2.0 equiv, dienophile, MS 4 Å, rt then reflux.

To verify this isomerization and also the stereochemical outcome of the reaction, single crystals of cycloadduct **18** were grown and an X-ray crystal structure was obtained. As can be seen in Figure 1, compound **18** results from an *endo* transition state followed by olefin isomerization. The stereochemistry of the cycloadducts in Table 3 were assigned by analogy.

As this method proved to be efficient over a broad array of substrates, we envisioned the possibility of applying it to a convergent synthesis of indolocarbazole alkaloids.[22,23] This

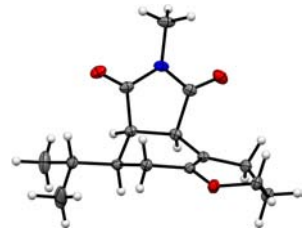


Figure 1. X-ray structure of compound **18**.

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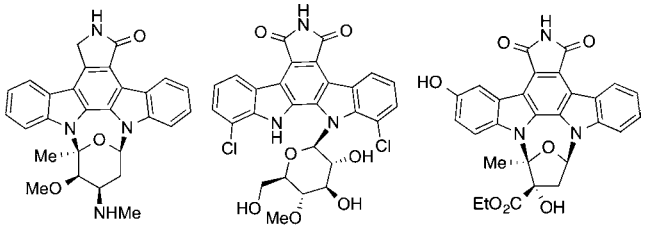
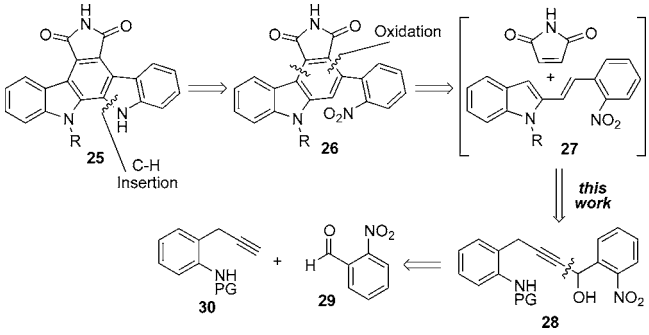
family of compounds exhibits a wide range of biological activities and has garnered attention from the synthetic[23] and biological communities.[24] Structurally, these compounds comprise an indolocarbazole core substituted with an N-linked carbohydrate and a fused amide or imide as seen below.[22] Both synthetic and naturally occurring variants are known in all three domains.[22] Well-known examples include staurosporine and rebeccamycin, but we were interested in developing an approach that could be applied to the indocarbazostatins, which are nanomolar inhibitors of nerve-growth-factor-induced neurite outgrowth.[25] These are particularly interesting as up-regulated neurotrophic factors have been observed in patients with epilepsy[26] and rat models of Huntington's disease.[27]



From a synthetic standpoint, we postulated that the indolocarbazole core of this family of alkaloids could be accessed from the Au-catalyzed cyclization/Diels–Alder methodology developed here by gaining rapid access to intermediate **26** (Scheme 2). The Diels–Alder reaction between diene **27** and

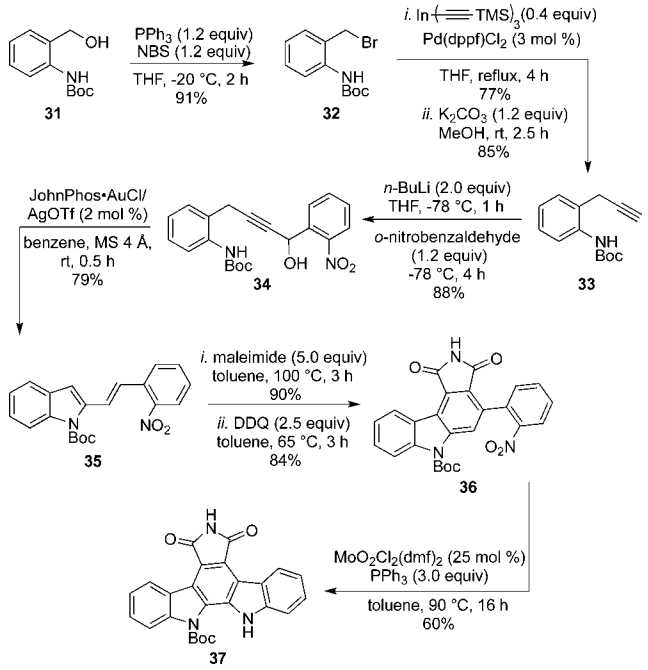
Scheme 2. Retrosynthetic Plan



maleimide would furnish all the carbon atoms necessary for the arcyriaflavin A skeleton **25** (R = H), necessitating CH insertion to form the final carbon–nitrogen bond. The key diene intermediate **27** would be obtained from the Au-catalyzed cyclization of substrate **28**, which would be derived from a simple alkynylation of an aldehyde with an alkyne. This synthetic strategy was designed to assemble the indolocarbazole core from three different components to allow for future syntheses by varying substitution on these fragments; furthermore, the design also allows for differentiation of the indole nitrogen atoms when substitution on the aromatic moieties differs as is seen in indocarbazostatin. This is an important feature for regioselective introduction of the carbohydrate fragment.

Synthesis of the key intermediate for Au-catalyzed diene formation and subsequent Diels–Alder reaction began with the known Boc-protected 2-aminobenzyl alcohol **31** (Scheme 3).[28] Conversion to the requisite alkyne **33** was achieved in a straightforward manner by bromide formation and palladium-catalyzed cross-coupling with tris(trimethylsilylacetylene)-indium,[29] followed by TMS deprotection with K_2CO_3 in MeOH. This three-step process was quite efficient, producing

Scheme 3. Synthesis of Boc-Protected Arcyriaflavin A



the respective products in 91, 77, and 85% yields. Deprotonation and acetylide addition to 2-nitrobenzaldehyde furnished the alkyne substrate **34** for the Au-catalyzed cyclization in 88% yield. At the outset, it was unclear if this substrate would be suitable for the dehydrative cyclization, but under the optimized conditions, diene **35** was smoothly formed in 79% yield. The Diels–Alder adduct was then obtained in 90% yield after heating the vinyl indole **35** with maleimide in toluene at 100 °C followed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone oxidation to afforded **36** in 84%. It was found to be convenient to isolate and purify **35** prior to the cycloaddition/oxidation sequence for ease of handling.

To complete the sequence, what remained was the final nitrene insertion step to form the C–N bond. Unfortunately, this was not easily achieved, and a large number of conditions were screened to no avail. The methods examined for this transformation ranged from using trivalent organophosphorous reagents[30] or Grignard reagents for reductive cyclizations[31] to a variety of contemporary catalytic and oxidative amination methods on modified substrates.[32−34] Fortunately, it was found that this key transformation could be accomplished in 60% yield using the $MoO_2Cl_2(dmf)_2$ catalyst[35] with triphenylphosphine to yield the nonsymmetrical arcyriaflavin A product **37**. Dichlorodioxomolybdenum(VI) complexes are interesting oxo-transfer catalysts reported for processes including the oxidation of thiols,[36] deoxygenation of sulfoxides,[37] and reduction of *N*-oxides.[38] The molybdenum catalyst was easily prepared in near quantitative yields from inexpensive starting materials.[37] Attempts at this cyclization in the absence of the molybdenum catalyst resulted in decomposition and/or partial deprotection of the Boc group. This approach should be advantageous for the synthesis of nonsymmetric, monoprotected analogues of these alkaloids such as the indocarbazostatins since it allows for regioselective introduction of a carbohydrate moiety.

In summary, a novel tandem Au-catalyzed cyclization/Diels–Alder method for the construction of bicyclic ring systems has been developed. The process, which proceeds from readily

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available starting materials, is efficient and high yielding and is advantageous because it avoids the isolation of sensitive 2-oxodienes. Using the new methodology, an approach to the synthesis of monosubstituted indolocarbazoles was accomplished. The synthetic design allows for differentiation of the indole nitrogens so that further functionalization could be performed regioselectively. We believe that this strategy will be highly applicable to natural product synthesis and, by its convergent nature, also provide access to highly diverse analogues. These studies are underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data, ^{1}H and ^{13}C NMR spectra, and HRMS for all novel compounds. CIF information for compound **18** is also provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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