Organic LETTERS

Letter

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β-Silyl-Assisted Tandem Diels–Alder/Nazarov Reaction of 1-Aryl-3-(trimethylsilyl) Ynones

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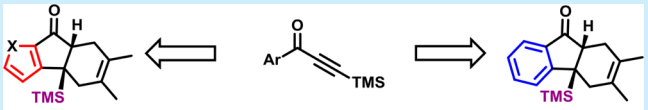
Supporting Information

ABSTRACT: A one-pot tandem Diels–Alder/Nazarov reaction of 1-aryl-3-(trimethylsilyl) ynones has been achieved to generate carbo- and heterocyclic fused ring systems in good to excellent yields. The β-silyl effect is instrumental in accessing this otherwise challenging cascade annulation reaction. The tandem reaction proceeds in the presence of BCl_3 to generate three new carbon–carbon bonds, a quaternary carbon, and two stereogenic centers with excellent diastereocontrol. A variety of substituted arenes, and even heteroaromatics, are tolerated to provide tricyclic products that are of interest as advanced intermediates toward biologically relevant compounds.



Simple starting materials for one-pot rapid access to highly modifiable core structures of biologically active natural products.

The design of efficacious synthetic methodology is integral to pharmaceutical development as well as expanding the frontiers of synthetic organic chemistry.[1] Terpenoids and related structures have a rich history for piquing the interest of synthetic groups, primarily due to the interesting biological activities inherent in many of these compounds.[2] Fused five- and six-membered polycyclic ring systems comprise the basic structure for a large number of important biologically active molecules.[3] New and efficient methods for the rapid construction of polycyclic substructures are highly sought after as a means to achieve more economical syntheses of naturally occurring or derivatized compounds of interest.[4] One can achieve this through the use of multicomponent and/or tandem reaction processes, and in the case of polycyclic compound synthesis this would likely involve an annulation step. The Nazarov cyclization is a synthetically valuable reaction toward cyclopentenones, and while a general catalytic asymmetric strategy has not yet been developed,[5] significant advancements have been made in regard to the Nazarov reaction.[6] There has been considerable interest in an aryl Nazarov cyclization as this bond formation is viewed by some as an essential step in the syntheses of several biologically important naturally occurring compounds.[7] However, the formation of the five-membered rings through a Nazarov cyclization involving aryl substrates is a synthetically challenging feat, requiring either dication intermediates via superacids[8] or highly activated substrates.[9] The Frontier group has conducted impressive studies on an Ir(III)-catalyzed Nazarov cyclization of polarized aryl vinyl ketone substrates (Figure 1a).[10] Photolysis has been successfully used by Smith and Agosta with aryl vinyl ketones to form a new five-membered ring embedded within a [6–5–6] polycyclic framework.[11] The Gao group has expanded the substrate scope of the photo-Nazarov reaction to a variety of substituted arenes and heteroaromatics (Figure 1b).[12] In many cases, the aryl vinyl ketone substrate for the Nazarov reaction must be synthesized with a heavy bias toward reactivity; otherwise, the Nazarov cyclization is unlikely to be the favored pathway. A more general method that can tolerate a variety of aryl vinyl ketone substrates, and additionally can be coupled with a multicomponent and/or tandem reaction event starting from relatively simple substrates, would be highly attractive for arriving at these useful synthetic scaffolds.

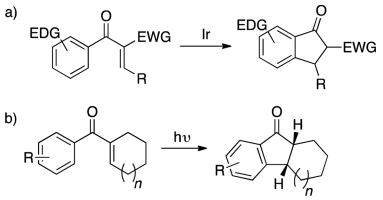


Figure 1. (a) Nazarov cyclizations of polarized aryl vinyl ketones through an iridium catalyst.[10] (b) Photo-Nazarov cyclization of diversified aryl vinyl ketones.[12]

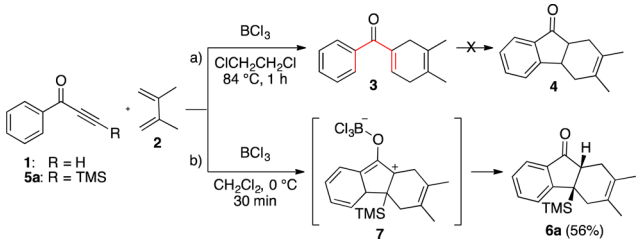
Our research endeavors are directed toward method development for rapidly accessing biologically interesting polycyclic frameworks, via multicomponent and tandem reaction sequences, that starts from alkyne-containing substrates.[13] The use of high-energy alkyne- and polyyne-containing substrates provides the thermodynamic driving force for arriving at complex polycyclic products by way of multicomponent/tandem reaction sequences. We recently reported a novel one-pot method for the formation of [6–5–6] tricyclic products resulting from a multicomponent double Diels–Alder/Nazarov tandem reaction of cross-conjugated diynones.[13a,b] We were curious as to whether aryl-substituted ynones would also undergo a tandem Diels–Alder/Nazarov reaction. This would arrive at a [6–5–6]-tricyclic scaffold containing an aryl moiety, a structural characteristic present in the taiwaniaquinol family of biologically active natural

Received: March 27, 2017

DOI: 10.1021/acs.orglett.7b00911
Org. Lett. XXXX, XXX, XXX–XXX

products.[3a,14] Ynone starting materials such as **1** were of particular interest to us as they readily undergo Diels–Alder cycloadditions with **2** to form a skipped diene intermediate **3**. We noted that compound **3** contains the necessary functionality to participate in a Nazarov cyclization (shown in red) (Scheme 1a, R = H) and wondered if we could effect this

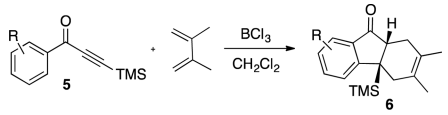
Scheme 1. Tandem Diels–Alder/Nazarov Reaction

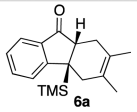
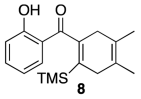
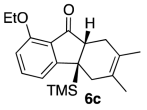
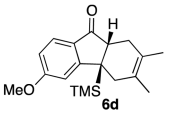
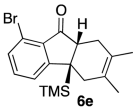
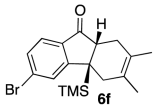
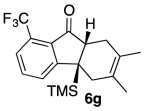
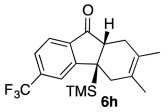
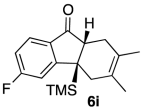
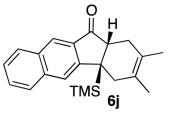


transformation to give **4**. We have previously screened Lewis acids that promote the alkyne Diels–Alder cycloaddition along with subsequent reactions and have found aluminum and boron Lewis acids to be most suitable.[13] We observed that the Diels–Alder product **3** formed rapidly with both aluminum and BCl_3. However, we did not observe any formation of the desired product **4** and more forcing conditions resulted in decomposition of **3**. In a previous study, we observed that silyl-substituted diynones demonstrated increased reactivity in both the Diels–Alder and Nazarov reaction.[13a,b] Since silyl substitution can have a strong stabilizing effect on the oxyallyl cation intermediate via the β-silyl effect,[15] we wondered whether silyl group incorporation onto the terminus of the ynone would sufficiently stabilize the reaction intermediates, enabling the Nazarov reaction to proceed under more mild conditions. Indeed, silyl-substituted ynone **5a** underwent the tandem Diels–Alder/Nazarov reaction rapidly to generate the desired product **6a** in good yield (56%) and excellent diastereoselectivity (>20:1, based on GC–MS analysis), presumably via the oxyallyl cation intermediate **7** (Scheme 1b). The *syn* relationship between the methine hydrogen and the TMS group was confirmed by 2D NOESY NMR spectroscopic analysis. Although desilylation is typical in other Nazarov reactions resulting in excellent regiocontrol of the resulting double bond,[13a,b,15] rearomatization via loss of a proton is preferred in this case, leaving the TMS group intact. A stoichiometric amount of Lewis acid was necessary for full conversion of the starting material, a requirement that has often been reported for Nazarov cyclizations.[5,13a,b]

Having established the proof of concept, we began looking at the scope of this reaction (Table 1). We first looked at electron-rich aryls, and although the *o*-methoxy-substituted ynone **5b** rapidly formed the Diels–Alder adduct, it was not surprising that this intermediate was demethylated[7a] to provide compound **8** in 75% yield with no formation of the Nazarov product (entry 2). We opted for a slightly bulkier ethyl group (**5c**, entry 3) in an attempt to minimize dealkylation, but this pathway was still faster than the Nazarov step, resulting only in the formation of **8**. Interestingly, $EtAlCl_2$ proved ineffective to promote the Nazarov cyclization for both **5b** and **5c**. The use of $AlBr_3$ also effected the demethylation side reaction of **5b** to provide only compound **8**. However, using $AlBr_3$ with **5c**, we did obtain desired product **6c**, albeit in poor yield (entry 3). The *p*-methoxy-substituted ynone **5d** successfully underwent the Diels–Alder/Nazarov reaction to generate **6d** in modest

Table 1. Substrate Scope of Ynone 5 for the Tandem Diels–Alder/Nazarov Reaction



entry	substrate	R	product	yield, %[a]
1	**5a**	H	 **6a**	56
2	**5b**	*o*-MeO	 **8**	75[b]
3	**5c**	*o*-EtO	 **6c**	17[c]
4	**5d**	*p*-MeO	 **6d**	44
5	**5e**	*o*-Br	 **6e**	51
6	**5f**	*p*-Br	 **6f**	63
7	**5g**	*o*-CF_3	 **6g**	26
8	**5h**	*p*-CF_3	 **6h**	63
9	**5i**	*p*-F	 **6i**	71
10	**5j**	-	 **6j**	57

[a]Isolated yield. [b]Isolated yield of compound **8**. [c]Yield of **6c** using $AlBr_3$. Note: A significant amount of product **8** was also detected at the end of the reaction.

yield (entry 4). It is not surprising that electron-donating groups (EDG) in the *ortho* and *para* positions (**5b–d**) perform poorly as they are less reactive dienophiles for the Diels–Alder cycloaddition and they inductively deactivate the aryl carbon

DOI: 10.1021/acs.orglett.7b00911
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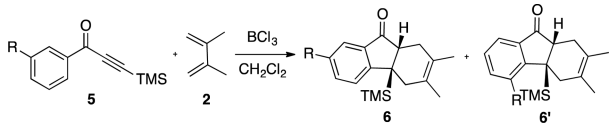
undergoing the rate-determining Nazarov cyclization. We were pleased that bromine-substituted ynones **5e** and **5f** both reacted to give compounds **6e** and **6f** in 51% and 63% yield, respectively, as these products will be suitable for subsequent transition-metal-catalyzed coupling reactions (entries 5 and 6). Having an electron-withdrawing group (EWG) in the *ortho*-position (**5g**) resulted in significant decomposition with only 26% yield of **6g** being isolated (entry 7). However, the electron-poor *para*-substituted ynone **5h** successfully gave **6h** in very good yield (entry 8). Fluorinated compounds have considerable importance in biologically active molecules, and as such, we were pleased to observe that substrate **5i** underwent the tandem Diels–Alder/Nazarov reaction quickly to form **6i** in excellent yield (entry 9). The naphthyl-substituted ynone **5j** was also tolerated and rapidly generated **6j** in 57% yield (entry 10).

We also decided to look at *meta*-substituted aryl ynones in order to gain insight into the regioselectivity of the Nazarov step with regard to these substrates (Table 2). Once again,

Table 2. Regioselectivity of *Meta*-Substituted Aryl Ynones



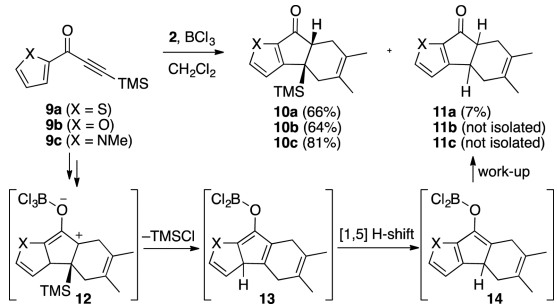
entry	R	product	yield[a] (%)	6/6′[b]
1	MeO (**5k**)	**6k**	trace	
2	MeO (**5k**)	**6k**	72[c]	15:1
3	CF_3 (**5l**)	**6l**	47[d]	45:1
4	CH_3 (**5m**)	**6m**	41	10:1
5	Cl (**5n**)	**6n**	44[d]	3:1

[a]Isolated yield. [b]Regioisomeric ratio of crude products determined by GC–MS analysis. Stereochemistry of minor regioisomers was assigned by analogy. [c]Using $AlBr_3$. [d]Isolated yield as an inseparable mixture of regioisomers (**6**/**6′**).

demethylation occurred over the course of the reaction for substrate **5k** when using BCl_3, resulting in only trace amounts of **6k** (entry 1). However, using $AlBr_3$ resulted in the formation of desired product **6k** in excellent yield with excellent regioselectivity (entry 2). Both the trifluoromethyl- and methyl-substituted ynones, **5l** and **5m**, reacted to generate the Nazarov products **6l** and **6m**, in modest yields 47%, and 41%, respectively (entries 3 and 4). Chloro-substituted ynone **5n** provided product **6n** in modest yield as an inseparable 3:1 mixture of regioisomers (entry 5). This decrease in regioselectivity can possibly be attributed to a steric effect as cyclization at C-2 of the aryl would be relatively easier in **5n** on account of the smaller chlorine substituent at C-3. Our observations suggest that having an EDG *para* to the carbon that is making the C–C bond during the rate-determining Nazarov cyclization (and *meta* to the carbonyl) increases the rate of the reaction and the yield.

We were interested to see whether heteroaryl-substituted ynones would also participate in the tandem Diels–Alder/Nazarov reaction (Scheme 2). Thiophene-substituted ynone **9a** rapidly underwent the tandem reaction to give **10a** in 66% yield.[16] The furan-substituted ynone **9b** also worked to provide **10b** in good yield.[17] We were very excited that the *N*-methylpyrrole derivative **9c** was also successful in this reaction to provide **10c** in good yield. It should be noted that we observed an unexpected minor side product in these reactions,

Scheme 2. Tandem Diels–Alder/Nazarov Reaction of Heteroaryl-Substituted Ynones



determined to be desilyated products **11a–c**. While **11a** was isolated in 7% yield (relative stereochemistry not determined) and **11c** was only detected in a trace amount, we were unable to isolate **11b** due to its decomposition upon attempted isolation. A plausible explanation for the formation of desilylated product **11** is that, due to the less aromatic character of these heteroaryl systems, the rate of desilylation in the oxyallyl cation intermediate **12** becomes competitive with the rate of deprotonation/rearomatization, as seen in analogous systems.[15d] A subsequent [1,5]-hydride shift in **13** to re-establish aromaticity followed by protonation of **14** during workup would provide product **11**. Nonetheless, we were pleased that the heteroaryl-substituted ynones reacted to generate an interesting class of [5–5–6] heterotricyclic ring systems.

In conclusion, we have demonstrated a tandem Diels–Alder/Nazarov reaction of 3-(trimethylsilyl)-1-aryl and 3-(trimethylsilyl)-1-heteroaryl ynones to yield biologically important polycyclic scaffolds in a one-pot reaction. Additionally, we have shown that our method can be applied to a variety of substituted ynones, allowing for extensive modification of the core structure. The one-pot tandem Diels–Alder/Nazarov reaction is highly regio- and diastereoselective, providing concise and efficient access to broad structural diversity while also imparting useful functional handles (arene, alkene, TMS, and ketone) for further chemical elaboration.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00911.

Experimental procedures and compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

W.A.C. acknowledges the National Science Foundation for supporting this work through a CAREER Award (CHE-1555218). This material is based upon work supported by the

DOI: 10.1021/acs.orglett.7b00911
Org. Lett. XXXX, XXX, XXX–XXX

National Aeronautics and Space Administration under Grant No. NNX10AN23H issued through the Nevada Space Grant Program (R.A.C.). We thank Casey Philbin (University of Nevada, Reno) for assisting with mass spectra data collection.

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(17) The ratio of the crude product mixture of **10b**/**11b** was determined to be 4:1 by GC−MS analysis.

DOI: 10.1021/acs.orglett.7b00911
Org. Lett. XXXX, XXX, XXX−XXX