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Tandem Nazarov Cyclization−Michael Addition Sequence Catalyzed by an Ir(III) Complex

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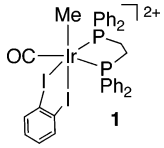
Catalytic Nazarov cyclizations using several different Lewis acid promoters have recently been described.[1] The cationic Ir(III) complex **1** as its $BAr^f{}_4^-$ salt is a very efficient catalyst for this reaction, and through its ability to engage in two-point binding of alkylidene β-ketoester substrates **2**, it promotes favorable conformations for cyclization to yield β-ketoester Nazarov products **3** (Table 1).[2] Reports of Michael addition reactions of β-ketoesters catalyzed by Lewis acids, such as palladium,[3] scandium,[4] copper,[5] aluminum,[6] nickel,[7,8] and magnesium[9] complexes, suggested to us that a tandem Nazarov cyclization−Michael addition process might be possible using complex **1**. In this communication, we report the successful development of this reaction sequence, which gives cyclopentenones **4** directly from precursors **2** in high yield, creating three contiguous stereocenters with excellent diastereoselectivity.[10]



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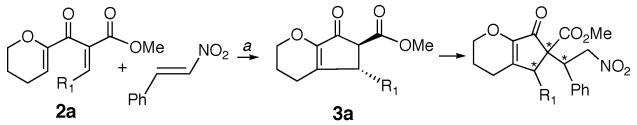
Initial exploratory studies found that while combinations of alkylidene β-ketoester **2a** and nitrostyrene with copper triflate, magnesium perchlorate, or **1** as catalyst yielded only Nazarov product **3a**, addition of *N*-methylmorpholine[9] to these reactions led to a mixture of two Michael addition product diastereomers (Table 1). With magnesium perchlorate or **1** as catalyst, the diastereomeric ratio increased with prolonged stirring (Table 1, entries 2 and 3). The observation of some decomposition of catalyst **1** in the presence of *N*-methylmorpholine (detected by ^{31}P NMR) stimulated a brief screening of amine bases in order to identify one that would be more compatible with complex **1**. It was found that *N*-ethylpiperidine (EPP) performs extremely well in this role. The tandem reaction was complete after 3 h, and the diastereomeric ratio improved to 14:1 after a total of 11.5 h (entry 4).[11] Both base and catalyst **1** are necessary for an efficient tandem reaction; if no base is added, only Nazarov product **3a** is formed, and in the absence of **1**, the reaction between **3a**, nitrostyrene, and *N*-ethylpiperidine (10 mol %) is very slow.[12]

It was possible to isolate the major diastereomer in nearly pure form by fractional recrystallization using an ethyl acetate/hexane mixture (see Supporting Information). In this way, a 14:1 mixture of Nazarov−Michael diastereomers (Table 1) was enriched to a 43:1 mixture, allowing crystallographic characterization of the major diastereomer **4a** (Figure 1). The same relative stereochemistry was found in tandem products **4b** and **4g** (Table 2), indicating that Michael addition occurs *anti* to the R_1 group of β-ketoesters **3**.[13]

Table 1. Optimization of Tandem Nazarov Cyclization/Michael Addition Sequence



2a **3a**

R_1= 4-methoxyphenyl

entry	catalyst	base[b]	dr (time)	yield
1	$Cu(OTf)_2$ (10 mol %)	A	3.4:1 (48 h)	
2	$Mg(ClO_4)_2$ (10 mol %)	A	3:1 (11 h)[c]	→
			5:1 (72 h)	80%
3	**1** (4 mol %)	A	1.7:1 (10 h)[c]	→
			5:1 (72 h)	88%
4	**1** (4 mol %)	B	2:1 (3 h)[c]	→
			14:1 (11.5 h)	92%

[a] Reaction conditions: 1,2-dichloroethane (0.20 M); 40 °C. [b] A = *N*-methylmorpholine; B = *N*-ethylpiperidine (EPP); 10 mol %. [c] About 95% conversion to tandem Nazarov−Michael addition products by ^{1}H NMR.

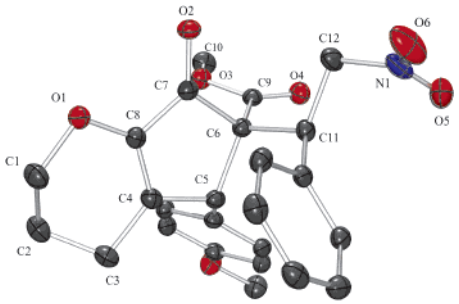


Figure 1. POVRAY representation of the major diastereomer (**4a**).

The reaction sequence showed similar efficiency and diastereoselectivity for a range of alkylidene β-ketoesters and nitroalkenes (Table 2). In every case, the reaction was highly diastereoselective, with only two of four possible diastereomers observed. The product mixture was isolated in high yield, and it was gratifying to find that alkyl substitution on the nitroalkene did not significantly decrease yield or selectivity (entry 5), and that alkylidene β-ketoesters with alkenyl substitution also gave good results (entry 9).

While it is possible that the Michael addition step of the tandem chemistry occurs via attack of enolate species **A** on free nitroalkene (Scheme 1), analogous to previously reported conjugate addition reactions of transition metal-complexed enolates,[1−3,8,9,14] the rapid rate of Michael addition suggests Lewis acid activation of the nitroalkene via formation of an enolate complex of type **B**.[15] The proposed ligand exchange is consistent with the exchange chemistry seen for **1** with η^1 intermediates of bidentate ligand species readily seen and would provide a more reactive enolate nucleophile and a coordination site to activate the nitroalkene electrophile.[16] Either intramolecular (shown) or intermolecular alkylation could then

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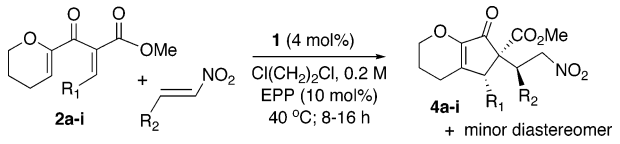
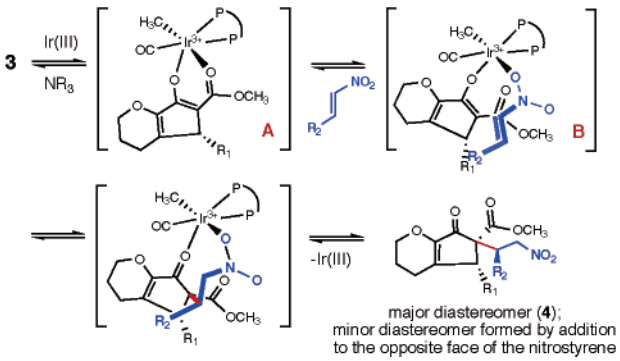
Table 2. Scope of Tandem Nazarov/Michael Addition Sequence[a]



entry	R_1	R_2	% yield[b] (product)	dr
1	4-methoxyphenyl	Ph	92 (**4a**)	14:1
2	4-methoxyphenyl	4-bromophenyl	90 (**4b**)	15:1
3	4-methoxyphenyl	4-methoxyphenyl	90 (**4c**)	13:1
4	4-methoxyphenyl	2-furyl	91 (**4d**)	12:1
5	4-methoxyphenyl	*n*-C_3H_7	85 (**4e**)	10:1
6	2-furyl	Ph	89 (**4f**)	13:1
7	2-furyl	4-bromophenyl	91 (**4g**)	15:1
8	2-furyl	4-methoxyphenyl	86 (**4h**)	13:1
9	cinnamyl	Ph	87 (**4i**)	8:1

[a] EPP = *N*-ethylpiperidine. [b] Isolated yield calculated from **2a**−**i** after column chromatography.

Scheme 1. Proposed Mechanism of the Tandem Nazarov Cyclization−Michael Addition Sequence[a]



[a] Formal charges on the nitro group omitted for clarity.

occur to give product. The tandem product **4** is expected to have a lower affinity for **1** relative to Nazarov product **3**, facilitating turnover of the catalyst.

Initially, two different pathways could be proposed to account for the thermodynamic equilibration of the product mixture.[17] Epimerization at C5 through a γ-enolate species constitutes one possibility, while the other involves isomerization of the C6 and/or C11 centers via reversible Michael reaction (see Figure 1 for carbon numbering). The following experiment distinguished the operative pathway. When a 1.6:1 mixture of tandem products was subjected to the reaction conditions containing ~20 equiv of CD_3-OD, free nitrostyrene and **3** were observed by ^{1}H NMR spectroscopy after 30 min, while the ratio of product diastereomers increased to 2.3:1. After 12 h, product equilibration was complete, and again, a 14:1 ratio of product diastereomers was observed, and no deuterium had been incorporated into the C5 position. Both observations support equilibration via reversible Michael addition rather than by γ-enolate formation.

The observed mixture of diastereomers results from either (a) Michael addition to one face of the nitroalkene from *both* faces of the enolate (i.e., C6−C11 bond formation *syn* vs *anti* to R_1) or (b) Michael addition to *both* faces of the nitroalkene from one face of the enolate. Because the structure of the minor diastereomer has not been determined, it is not yet possible to rule out either pathway as the route dictating the diastereoselectivity. However, since kinetic protonation of enolates of type **A** more often occurs *anti* to R_1[2] and the Michael acceptor in these reactions is larger than a proton or proton source, Michael addition *anti* to R_1 should be strongly favored. This is consistent with the stereochemistry of the crystallographically studied major diastereomers **4**. Simple models indicate that both faces of the nitroalkene should be accessible for Michael addition *anti* to R_1 of **3**, and consistent with this proposal, ^{1}H NMR data show that the C12 (α-nitro) protons of the minor diastereomer are shifted significantly because of addition to the other face of the Michael acceptor. This reasoning leads to the conclusion that diastereoselection occurs via pathway (b), giving products with different relative stereochemistry at C11 only.

In summary, we report the first examples of a tandem Nazarov cyclization/Michael addition process. The sequence is efficiently catalyzed by Ir[Me(CO)(dppe)(DIB)]$^{2+}$ and occurs with high diastereoselectivity, creating three new stereocenters. Further exploration of the scope and mechanism of the sequence, as well as application to natural product synthesis, is in progress in our laboratories.

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Supporting Information Available: General experimental procedures, characterization data for compounds **4a**−**4i**, and X-ray crystallographic data for compounds **4a**, **4b**, and **4g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) When *N*-ethylpiperidine was used as the base with $Mg(ClO_4)_2$ as catalyst, reaction was slow with poor conversion after 3 days.
(12) Less than 5% conversion was observed after 4 h at 45 °C.
(13) X-ray crystal structures collected for products **4b** and **4g** (Table 2, entries 2 and 7) indicated the same relative stereochemistry as **4a** (see Supporting Information).
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(17) Product equilibration was also observed by Barnes and Ji (ref 9).

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