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Divergent Reaction Pathways of a Cationic Intermediate: Rearrangement and Cyclization of 2-Substituted Furyl and Benzofuryl Enones Catalyzed by Iridium(III)

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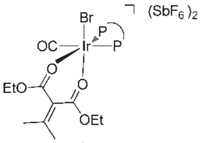
Supporting Information

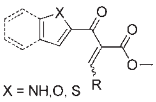
ABSTRACT: In contrast to 2-substituted pyrrole enones, furyl and benzofuryl enones do not undergo the Nazarov electrocyclization. Instead, these furyl and benzofuryl enones exhibit unusual rearrangement sequences in the presence of catalytic amounts of [IrBr(CO)(DIM)((*R*)-(+)-BINAP)]$(SbF_6)_2$ (**1**; DIM = diethylisopropylidene malonate) and $AgSbF_6$ (1:1). A 1,2-H shift followed by intramolecular Friedel−Crafts alkylation leads to synthetically valuable cyclohexanones with furanylic quaternary centers. The electrophilicity of **1** is essential for this rearrangement.

The Nazarov cyclization[1] of polarized divinyl or aryl vinyl ketones[2] to form densely functionalized cyclopentenones has been achieved with a number of catalysts.[2,3] The reaction proceeds via the formation of a pentadienyl cation intermediate that undergoes electrocyclization. Complex **1**, which is activated by bromide abstraction using $AgSbF_6$ to generate a tricationic d^6 iridium species, is able to effect cyclization in some of the most unreactive molecules.[3q] The Nazarov cyclization of heteroaromatic enones of type **A** has been previously achieved using catalytic $Sc(OTf)_3$ and a stoichiometric amount of $LiClO_4$.[3d] The reaction is efficient for indole and pyrrole (e.g., Table 1, entry 1), but the analogous furyl and benzofuryl enones do not undergo similar cyclizations.[3d] The difficulty associated with these cyclizations prompted us to examine the effect of tricationic **1**/$AgSbF_6$ on potential furan and benzofuran substrates of type **A**. The study described in this communication reveals that furans and benzofurans of type **A** follow a fundamentally different reaction pathway than pyrroles, indoles, and thiophenes of type **A** when subjected to iridium(III) catalyst **1**.



1

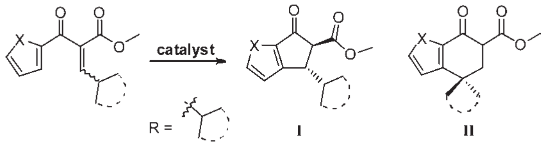
P P = (*R*)-(+)-BINAP



A

When **2** (R = ^{i}Pr; Table 1, entry 3) was treated with **1** and $AgSbF_6$, a cyclization occurred, but it was not the expected four-π-electron Nazarov electrocyclization.[3d,3p,3q] Instead, cyclohexanone **II**, which contains a new quaternary carbon at the furanylic position, was the only product observed (>99% conversion as determined by ^{1}H NMR spectroscopy). In comparison, the reaction of **2** with $Sc(OTf)_3$/$LiClO_4$ gave a complex mixture of products, and cyclohexanone **II** was present only in small amounts (entry 4).

Table 1. Cyclization with 2-Substituted Pyrrole and Furyl Enones[a]



entry	X	R	catalyst[a]	product (% yield)
1	NH	cyclobutyl	$Sc(OTf)_3$/$LiClO_4$	**I** (61%)[b]
2	NH	cyclobutyl	**1**/$AgSbF_6$	**I** (71%)[b]
3	O	^{i}Pr	**1**/$AgSbF_6$	**II** (69%)
4	O	^{i}Pr	$Sc(OTf)_3$/$LiClO_4$	**II** (<10%)

[a] Reaction conditions: $Sc(OTf)_3$ (10 mol %)/$LiClO_4$ (1 equiv) or **1** (10 mol %)/$AgSbF_6$ (10 mol %), 80 °C, DCE or CD_3NO_2. [b] See ref 3q.

The unusual and selective reaction sequence observed when furanyl enone **2** was exposed to Ir(III) complex **1** encouraged us to investigate this transformation further. The scope of the cyclization was explored with a variety of 2-substituted furyl and benzofuryl enones (Table 2). The enone substrates were prepared in excellent yields using either oxidoalkylidenation of alkynes[4] or Knoevenagel condensation.[3d,5]

Reactions could be run at 80 °C but were most efficient at 100 °C. Furyl enone **2** furnished **3** at 100 °C in 8 h (Table 2, entry 1). Benzofuranyl enone **4** (R = ^{i}Pr) rearranged to **5** within 2 h with an excellent yield of 92% (entry 2). A methyl substituent at the 5-position of the furan ring in **6** (R = ^{i}Pr) had a parallel effect on the reaction time (entry 3). An extension of the reaction scope to cyclic precursors **8**, **10**, **12**, and **14** resulted in the formation of [5,5]- and [5,6]-spirocyclic scaffolds **9**, **11**, **13**, and **15** in high yields (70−83%; entries 4−7).

While enones with cyclohexyl and cyclopentyl side chains formed spirocyclic cyclohexanones, cyclobutyl substrates **16** and

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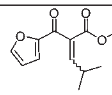
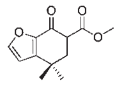
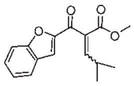
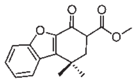
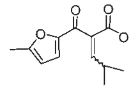
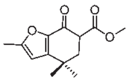
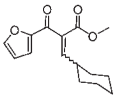
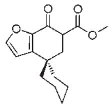
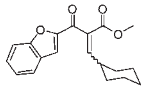
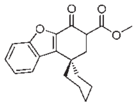
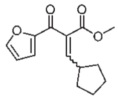
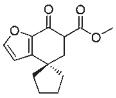
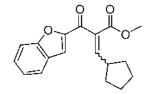
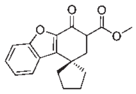
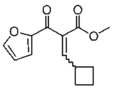
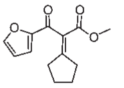
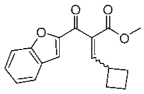
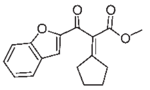
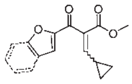
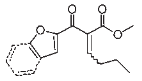
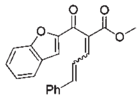
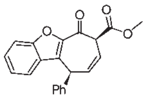
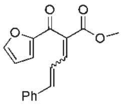
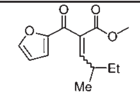
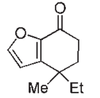
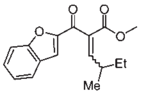
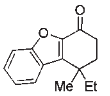
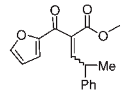
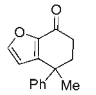
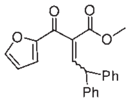
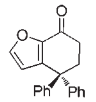
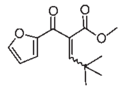
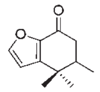
Table 2. Cyclization with 2-Substituted Furyl and Benzofuryl Enones[a]

entry	substrate	product	time[b] (h)	yield[c] (%)
1	 **2**	 **3**	48[d] 8	69 71
2	 **4**	 **5**	2	92
3	 **6**	 **7**	5	66
4	 **8**	 **9**	8	73
5	 **10**	 **11**	1.5	83
6	 **12**	 **13**	8	70
7	 **14**	 **15**	1.5	78
8	 **16**	 **17**	0.5[d]	99
9	 **18**	 **19**	0.5[d]	99
10	 **20**	-	24	-[e]
11	 **21**	-	10	-[e]
12	 **22**	 **23**	16	53
13	 **24**	-	24	-[e]

[a] Reaction conditions: 100 °C, **1** (10 mol %), $AgSbF_6$ (10 mol %), CD_3NO_2 (0.1 M), minimum light. [b] Reactions were monitored using ^1H NMR spectroscopy until >99% conversion was achieved. [c] Isolated yields. [d] Cyclization was performed at 80 °C. [e] Decomposition of substrate.

Table 3. Cyclization Followed by Decarboxylation[a]

entry	substrate	product	time[b] (h)	yield[c] (%)
1	 **25**	 **26**	8	76
2	 **27**	 **28**	1.5	81
3	 **29**	 **30**	1	70
4	 **31**	 **32**	16	67
5	 **33**	 **34**	24[d]	51

[a] Reaction conditions: (i) Cyclization: 100 °C, **1** (10 mol %), $AgSbF_6$ (10 mol %), CD_3NO_2 (0.1 M), minimum light. (ii) Decarboxylation: DABCO (0.5 equiv), toluene (0.1 M), H_2O (0.1 equiv), reflux. [b] Cyclization time for >99% conversion as determined using ^1H NMR spectroscopy. [c] Isolated yields over two steps. [d] Cyclization required 20 mol % **1** and 20 mol % $AgSbF_6$.

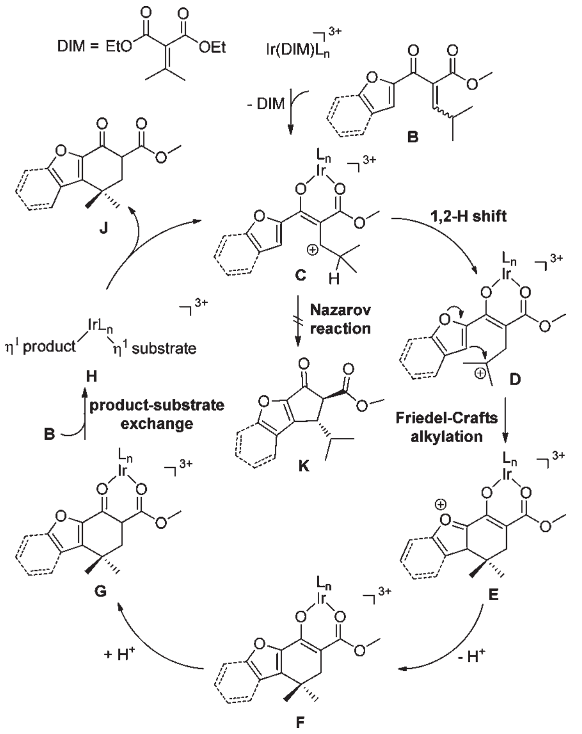
18 rearranged to form tetrasubstituted double bonds in **17** and **19** without further reaction even at elevated temperatures (entries 8 and 9). In contrast, the 2-substituted pyrrole enone with R = cyclobutyl undergoes simple Nazarov cyclization (Table 1, entry 2).[3q] Cyclopropyl and *n*-propyl variants (**20** and **21**) did not show the same reactivity (entries 10 and 11).

Benzofuryl dienone **22** underwent an unexpected six-π-electron ring closure to provide cycloheptenone **23** (entry 12). This is particularly interesting when viewed in the context of previous studies exploring the reactivity of vinyl dienyl ketones, in which Nazarov-type four-π-electron electrocyclization has been the only reaction observed.[2a,3q] Cyclization of the analogous furyl substrate **24** was not observed (entry 13).

A subsequent endeavor to cyclize furyl or benzofuryl enones with more elaborate side chains led to the isolation of cyclohexanones with new quaternary stereocenters (Table 3). Enones **25** and **27** generated their respective furyl and benzofuryl cyclohexanones in a diastereomeric ratio of 1:1. Quantitative decarboxylation of the product mixture using 1,4-diazabicyclo[2.2.2]-octane (DABCO) afforded **26** and **28**, respectively (entries 1 and 2). Enones **29** and **31** with phenyl-containing side chains furnished hydride migration products **30** and **32** (entries 3 and 4). Enone **33** (R = ^{t}Bu) underwent a 1,2-methyl shift to afford **34** upon decarboxylation (entry 5).

A mechanistic rationale for this Ir(III)-catalyzed rearrangement is outlined in Scheme 1. The catalysis is initiated with the displacement of the malonate from **1** and bidentate coordination of **B** to form pentadienyl cation **C**.[3b] A 1,2-hydride shift from the pendant side chain occurs, generating tertiary carbocation **D**. The formation of **D** induces an intramolecular Friedel−Crafts alkylation[6] at the 3-position of the furyl ring, leading to oxyallyl cation **E**. Subsequent elimination provides enolate **F**, and protonation forms the metal-bound species **G**. A product−substrate

Scheme 1. Divergent Reaction Pathways of the Pentadienyl Cation Intermediate with Iridium(III)

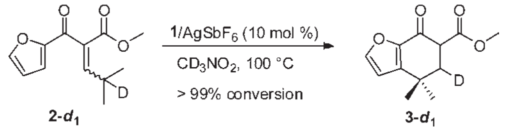


exchange step through η^1-coordinated Ir(III) species **H**[3b] furnishes furyl- or benzofuryl-fused cyclohexanone **J**.

Density functional theory (DFT) calculations [B3LYP with the 6-31G(d) basis set for C, H, O, N, and P and the LANL2DZ basis set for Ir] were performed on coordinated **2** as **C** or **D**. The energy of **D** was found to be 1.11 kcal/mol *lower* than that of **C**; this supports the mechanism, which invokes carbocation stability as a driving force for the hydride shift. Conversely, the tertiary carbocation of the pyrrole analogue is 1.72 kcal/mol *higher* in energy than the cyclopentadienyl carbocation, and only the Nazarov product is obtained. The gap between the highest occupied orbital with significant electron density on the furan 3-position and the lowest unoccupied orbital with contributions from the cationic carbon is 5.17 eV (HOMO-3 to LUMO+1) for **C** and 2.65 eV (HOMO to LUMO+1) for **D** (see the Supporting Information).

Other experiments conducted during the study were consistent with the proposed carbocationic mechanism. Benzofuran or furan **21** has an unbranched alkyl chain that provides no opportunity for the formation of a tertiary carbocation, and no cyclization was observed (Table 2, entry 11). In comparison, **33** with a branched alkyl chain underwent a 1,2-methyl shift to form a tertiary carbocation and subsequent cyclization product **34** (Table 3, entry 5). Similarly, compounds **16** and **18** underwent an alkyl shift with ring expansion, consistent with an intermediate carbocation similar to **D**, although the subsequent cyclization was not observed (Table 2, entries 8 and 9). To further probe the viability of the proposed 1,2-H migration, cyclization with a deuterated variant of **2** (**2-*d*$_1$**) was examined (Scheme 2). A 1,2-deuteride shift from the isopropyl chain of **2-*d*$_1$** to form **3-*d*$_1$** was confirmed using ^{2}H NMR spectroscopy. Simpler enones with branched alkyl chains are known to experience a 1,2-hydride shift upon treatment with protic acid and generate carbocation-trapped products.[7]

Scheme 2. Cyclization of a Deuterated Variant of 2



In conclusion, we have reported a novel rearrangement sequence involving a 1,2-H shift and a Friedel−Crafts alkylation sequence of 2-substituted furyl and benzofuryl enones using the electrophilic Ir(III) complex **1**. Pentadienyl cation intermediate **C** generated from heteroaryl vinyl ketones (Scheme 1) suffers a hydride shift rather than undergoing Nazarov electrocyclization. We are aware of only one transformation related to this one: a 1,2-H shift/Friedel−Crafts alkylation of indoles.[8] The sequence represents an efficient method for the preparation of furan- and benzofuran-fused cyclohexanone ring systems with quaternary centers, which are motifs found in various bioactive molecules.[9] Detailed studies of the mechanism and efforts directed toward achieving asymmetric Ir(III) catalysis are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental details, preparation and characterization of new compounds, and data from DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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