Communication

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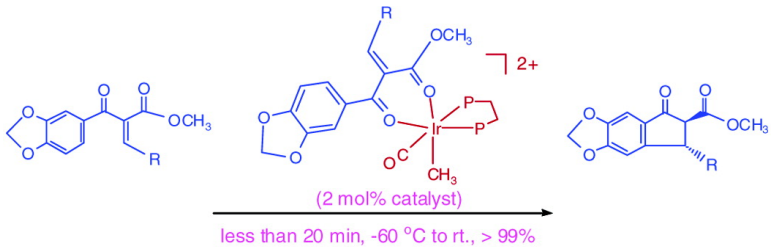

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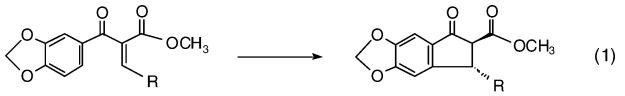
Efficient Catalysis of Nazarov Cyclization Using a Cationic Iridium Complex Possessing Adjacent Labile Coordination Sites

Mesfin Janka, Wei He, Alison J. Frontier,* and Richard Eisenberg*

Department of Chemistry, University of Rochester, Rochester, New York 14627

Received January 20, 2004; E-mail: frontier@chem.rochester.edu; eisenberg@chem.rochester.edu

The widespread occurrence of five-membered carbocycles in natural products and bioactive molecules has stimulated interest in utilizing Nazarov cyclization strategies for their synthesis.[1,2] This reaction is a 4π electrocyclization that can convert divinyl ketones into cyclopentenones stereoselectively via conrotatory cyclization. The Nazarov cyclization is generally promoted by one or more equivalents of a protic or Lewis acid (e.g., BF_3, $SnCl_4$, $TiCl_4$, or $AlCl_3$) and most often involves the intermediacy of a 3-oxypentadienyl cation. Several recent studies have focused on catalysis of the Nazarov cyclization using $Cu(OTf)_2$,[3] $PdCl_2(MeCN)_2$,[4] $Sc(pybox)(OTf)_3$,[5] and $Cu(pybox)(OTf)_2$[6] complexes, with modest asymmetric induction observed with the pybox systems. In one of these studies,[3] two of us examined polarization of Nazarov substrates with electron-rich and electron-poor vinyl groups as a means of obtaining good catalysis under mild conditions, as for example in eq 1 with Cu(II) triflate. In this Communication, we



(1)

R = 2,4,6-trimethoxyphenyl

report even higher reaction rates for catalysis of the Nazarov cyclization using the dicationic Ir(III) complex [IrMe(CO)(dppe)(DIB)](BARF)$_2$ (**1**) where dppe = bis(diphenylphosphino)ethane, DIB = *o*-diiodobenzene, and BARF = [B(3,5-$C_6H_3(CF_3)_2)_4$], as well as spectroscopic characterization of the substrate−catalyst complex and kinetics of the reaction.[7] Complex **1** has previously been described as an active electrophilic system capable of promoting olefin polymerization of isobutylene, vinyl ethers, and β-pinene by a cationic mechanism.[8,9] Despite the usual inertness of cationic octahedral d^6 metal complexes, the weak coordinating ability of the DIB ligand provides adjacent labile sites in **1** that are found to play a crucial role in the observed Nazarov electrocyclization.

Whereas eq 1 in the presence of 2 mol % of $Cu(OTf)_2$ at 53 °C for 20 h proceeds in 92% yield, the same reaction is quantitative in less than 20 min using 2 mol % of **1** at room temperature. The reaction was further examined by variable temperature ^{1}H and ^{31}P NMR spectroscopies. It was found by ^{31}P NMR spectroscopy that displacement of the DIB ligand by substrate is rapid and essentially complete at −10 °C, with some substrate binding observed at temperatures as low as −30 °C. The $^{31}P\{^1H\}$ spectrum at −10 °C (Figure 1) shows two pairs of doublets, assigned as regioisomeric complexes **2** and **3**.[10] Similar differential binding has been observed with the dienophile *N*-crotonyl-2-oxazolidinone.[11,12] In contrast, exchange of the DIB ligand of **1** with 1 equiv of the symmetrical chelating ligand dimethyl maleate forms only a single species based on the ^{1}H and $^{31}P\{^1H\}$ NMR data.[13]

The kinetics of the reaction shown in eq 1 catalyzed by **1** and measured using ^{1}H NMR spectroscopy indicate first-order dependence on both substrate and catalyst concentrations, indicating that product inhibition does not occur. The second-order rate constant for eq 1 at 15 °C was determined to be 112.5 M^{-1} min^{-1}.[14] On the basis of the kinetics and binding studies for the reactant of eq 1, a plausible mechanism for the process involves generation of the oxyallyl cation **4** (a resonance form is shown), cyclization to generate intermediate **5**, re-aromatization, enolate protonation to give catalyst-bound product, and substrate substitution to give free product and **4** (Scheme 1).

Further support for the proposed substrate binding and catalysis was obtained by studying various substrates **6**. For all of the polarized divinyl ketones **6** except **6f**, complex **1** (2 mol % in CH_2Cl_2) was found to catalyze the Nazarov cyclization essentially quanti-

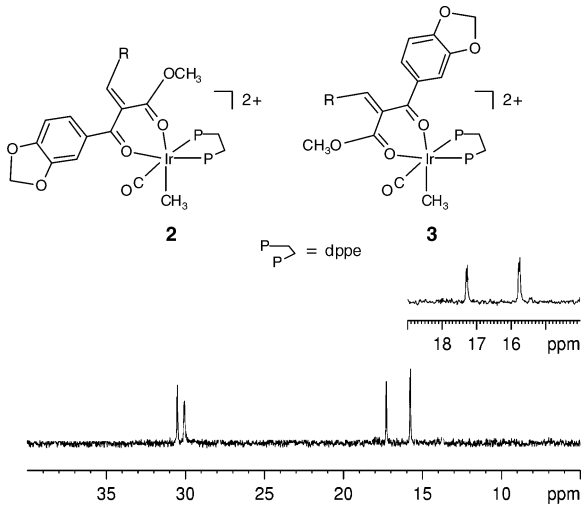
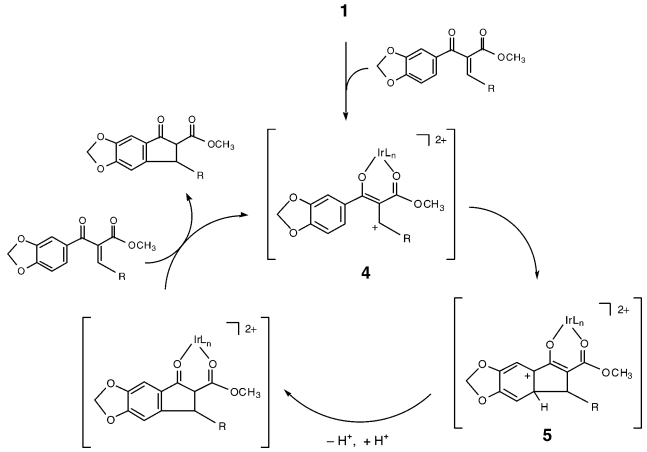


Figure 1. $^{31}P\{^1H\}$ NMR spectrum of Nazarov substrate 2-(benzo[1,3]-dioxole-5-carbonyl)-3-(2,4,6-trimethoxyphenyl)acrylic acid methyl ester and 2.0 mol % of catalyst **1** in CD_2Cl_2 at −10 °C.

Scheme 1



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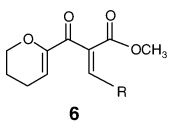
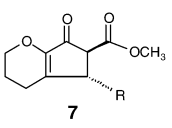
tatively to give **7** (> 99% yield) in less than 20 min upon warming to room temperature from −60 °C.[15] In comparison, cyclization of



6

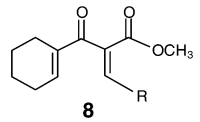


7

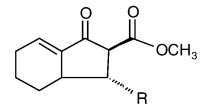
a R = 3-methoxyphenyl
b 4-methoxyphenyl
c phenyl
d 2-furyl
e 2,4,6-trimethoxyphenyl
f cyclohexyl

these substrates with $Cu(OTf)_2$ was significantly slower: for **6a** → **7a**, complete conversion required 48 h; for **6c** → **7c**, 108 h; and for **6d** → **7d**, 12 h at ambient temperature in dichloroethane. The least reactive substrate **6f**, which gave less than 50% yield after 240 h with $Cu(OTf)_2$,[3] was quantitatively converted to the cyclized product **7f** using **1** as the catalyst in less than 4 h at room temperature.

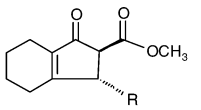
The importance of the adjacent labile binding sites of **1** and the nature of substrate chelation to **1** is illustrated by cyclization studies of specifically varied substrates. For example, substrate **8** cyclizes smoothly in the presence of 5 mol % of catalyst **1** at 45 °C in less than 1 h to produce the cyclohexene regioisomers **9a** and **9b**.



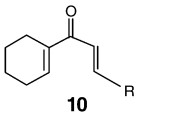
8
R = phenyl
5 mol% **1**, < 1 h, 45 °C



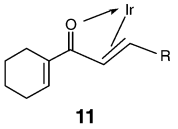
9a



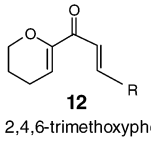
9b



10
R = 2,4,6-trimethoxyphenyl
NO CYCLIZATION with **1**



11



12
R = 2,4,6-trimethoxyphenyl
2 mol% **1**, < 0.4 h, -60 °C to rt.

However **10**, which undergoes smooth Nazarov cyclization with $Cu(OTf)_2$ (55 °C, 9 h, 53%), does not cyclize when treated with **1**.[16] ^{1}H NMR spectroscopy of the reaction solution reveals that **10** readily displaces the DIB chelate of **1**, while the $^{31}P\{^1H\}$ NMR spectrum shows two pairs of doublets in a 6.7:1 ratio, indicating two isomers from possible bidentate coordination.[17] The observation that **10** coordinates to **1** but does not cyclize suggests that in the absence of a second carbonyl the Ir(III) center may bind to an olefin of **10** instead, as shown in **11**. The two vinyl groups of **11** would be spatially separated and not in an orientation to allow for cyclization. Interestingly, substrate **12** cyclizes quantitatively in less than 20 min using 2 mol % of **1** upon warming to room temperature. The $^{31}P\{^1H\}$ NMR spectrum recorded at −20 °C before cyclization showed two pairs of doublets.[18] In this case, it appears that the carbonyl and ether oxygen atoms bind to the catalyst, allowing the two vinyl groups to adopt the proper orientation for cyclization.

In summary, we report that the electrophilic Ir(III) complex **1** having a labile DIB chelate is a very reactive catalyst for promoting the Nazarov cyclization of aryl vinyl and divinyl ketones. This is the first example of catalysis of the Nazarov cyclization using a well-defined cationic metal complex having two adjacent substrate binding sites. These studies have also allowed observation of the binding behavior of various divinyl ketone precursors to **1** prior to cyclization. Both the electrophilicity of cationic **1** and the lability of the cis binding sites play key roles in making **1** a highly effective catalyst. Detailed kinetic studies to further understand the mechanism of the cyclization and investigation of enantioselective Nazarov cyclization using chiral analogues of **1** are in progress.

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Supporting Information Available: Detailed experimental procedures and representative kinetic study graphs (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) We have been unable to confidently assign the olefin geometry of the starting substrates at this time.
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(10) $^{31}P\{^1H\}$ NMR (CD_2Cl_2) at −10 °C for the major isomer (55%): δ 30.5 (d, J_{P-P} = 4.8 Hz, 1P, *trans* to CO), 15.8 (d, J_{P-P} = 4.8 Hz, 1P, *cis* to CO). For the minor isomer (45%): δ 30.0 (d, J_{P-P} = 4.8 Hz, 1P, *trans* to CO), 17.3 (d, J_{P-P} = 4.8 Hz, 1P, *cis* to CO).
(11) For synthesis of *N*-crotonyl-2-oxazolidinone, see: Jaquith, J. B.; Levy, C. J.; Bondar, G. V.; Wang, S.; Collins, S. *Organometallics* **1998**, *17*, 914−925.
(12) $^{31}P\{^1H\}$ NMR (CD_2Cl_2) at 25 °C for the major isomer (66%): δ 32.7 (d, J_{P-P} = 4.7 Hz, J_{P-C} = 130 Hz, 1P, *trans* to CO), 15.1 (d, J_{P-P} = 4.7 Hz, 1P, *cis* to CO). For the minor isomer (34%): δ 31.9 (d, J_{P-P} = 4.7 Hz, J_{P-C} = 123 Hz, 1P, *trans* to CO), 15.9 (d, J_{P-P} = 4.7 Hz, J_{P-C} = 123 Hz, 1P, *cis* to CO).
(13) $^{31}P\{^1H\}$ NMR (CD_2Cl_2) at 25 °C: δ 33.6 (d, J_{P-P} = 4.7 Hz, 1P, *trans* to CO), 17.2 (d, J_{P-P} = 4.7 Hz, 1P, *cis* to CO).
(14) The rate constant for the same reaction using $Cu(OTf)_2$ as a catalyst at 75 °C is 7.6 M^{-1} min^{-1}.
(15) Each β-keto ester product **7** was isolated as a single regio- and stereoisomer with a *trans* relationship of the α and β substituents on the former vinyl electrophile and characterized as reported in ref 3.
(16) Substrate **9** does not cyclize when treated with **1** even with increased catalyst loading and longer reaction time at high temperature.
(17) $^{31}P\{^1H\}$ NMR (CD_2Cl_2) at −10 °C for the major isomer (87%): δ 24.1 (d, J_{P-P} = 6.0 Hz, 1P, *trans* to CO), 13.8 (d, J_{P-P} = 6.0 Hz, 1P, *cis* to CO). For the minor isomer (13%): δ 26.3 (d, J_{P-P} = 6.0 Hz, 1P, *trans* to CO), 18.4 (d, J_{P-P} = 6.0 Hz, 1P, *cis* to CO).
(18) $^{31}P\{^1H\}$ NMR (CD_2Cl_2) at −20 °C for the major isomer (67%): δ 31.7 (d, J_{P-P} = 4.8 Hz, 1P, *trans* to CO), 16.0 (d, J_{P-P} = 6.0 Hz, 1P, *cis* to CO). For the minor isomer (33%): δ 32.8 (d, J_{P-P} = 5.1 Hz, 1P, *trans* to CO), 16.0 (d, J_{P-P} = 5.1 Hz, 1P, *cis* to CO).

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