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A Highly Reactive Dicationic Iridium(III) Catalyst for Polarized Nazarov Cyclization

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Abstract

Pushing the Nazarov Envelope

A new electrophilic complex $[\text{IrBr}(\text{CO})(\text{diethylisopropylidene malonate})((R)\text{-(+)-BINAP})](\text{SbF}_6)_2$ (**2**) exhibits unusual activity in the catalysis of polarized Nazarov cyclization. Aryl vinyl ketones that show poor reactivity with well-known catalysts such as $[\text{Ir}(\text{CH}_3)(\text{CO})(1,2\text{-diiodobenzene})(\text{dppe})](\text{B}(\text{Ar}^f)_4^-)_2$ (**1**), $\text{Sc}(\text{OTf})_3 + \text{LiClO}_4$ and $\text{Cu}(\text{ClO}_4)_2$, can be cyclized with **2** + AgSbF_6 (1:1) under mild conditions with concurrent AgBr precipitation.

Keywords

electrophilic iridium; homogeneous catalysis; Lewis acids; non-coordinating anion; polarized Nazarov cyclization

Since the discovery of silicon-directed approach by Denmark,[1] the Nazarov reaction has been employed in the syntheses of a substantial number of natural products and bioactive molecules containing highly functionalized five-membered carbocycles.[2] Originally, stoichiometric or super-stoichiometric amounts of Brønsted or Lewis acids were required to promote the Nazarov cyclization of divinyl ketones and aryl vinyl ketones (aryl enones), generating cyclopentanones *via* a stereospecific 4π electrocyclization.[3] The efficacy of cyclization is enormously dependent on both the promoter and the electronic disposition of the substrate. With polarized substrates,[2a,4] catalytic cyclization is possible using $\text{Cu}(\text{OTf})_2$, [4b,5] $\text{Sc}(\text{OTf})_3$, [6] $\text{PdCl}_2(\text{MeCN})_2$, [7] or $\text{Cu}(\text{SbF}_6)_2$ [8] as a promoter. While moderate levels of asymmetric induction were achieved using $\text{Sc}(\text{pybox})(\text{OTf})_3$ [9] and $\text{Cu}(\text{pybox})(\text{OTf})_2$, [10] $[\text{Ni}(\text{bis}\{(R)\text{-1-}[(S)\text{-2}(\text{diphenylphosphino})\text{ferrocenyl}]\text{ethyl}\}\text{cyclohexylphosphine})(\text{THF})](\text{ClO}_4)_2$ offered notable enantioselectivity, but with slow cyclization rates.[11]

Cationic complexes of heavier platinum group metals have been extensively studied for electrophilically driven transformations.[12] In this context, Albeitz *et al.* reported the electrophilic complex $[\text{Ir}(\text{dppe})(\text{CH}_3)(\text{CO})(\text{DIB})](\text{B}(\text{Ar}^f)_4^-)_2$ (**1**), (where DIB = 1,2-diiodobenzene), which promotes olefin polymerization *via* a cationic mechanism.[13] Subsequently, **1** was found to catalyze the Nazarov cyclization[14] and a tandem Nazarov/

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Michael addition sequence[15] with significantly higher reaction rates and at lower temperatures, when compared to other Lewis acid catalysts.

Despite these successes using the highly active complex **1**, cyclization of aromatic substrates with -CN and -NO₂ groups could not be achieved and catalysis with -PO(OEt)₂ and -SO₂(*p*-tolyl) substituents was not efficient.[5] In order to obtain unusually functionalized cyclopentanones fused with aromatic or heteroaromatic residues, these limitations in scope represented a challenge to be addressed with a catalyst both more active and robust than **1**. Such cyclizations represent powerful strategies for syntheses of complex molecules and natural products such as roseophilin[16] and the tetrapetalone family.[17] To increase electrophilicity of the catalyst, a trication generated by Br⁻ abstraction was envisioned. This trication would be stabilized against decomposition by the bulkier di(phosphine) ligand BINAP.

This communication describes the synthesis and reactivity of [IrBr(CO)(DIM)((*R*)-(+)-BINAP)](SbF₆)₂·CH₂Cl₂ (**2**), (where DIM = diethylisopropylidene malonate), a new catalyst that exhibits truly notable activity. Extraction of Br⁻ ligand in **2** in conjunction with the lability of the DIM ligand creates a new way to generate extremely electrophilic d⁶ iridium species for electrocyclicization of aryl enones that cannot be activated otherwise. Through the use of **2**, the cyclization of these unreactive substrates to the desired cyclopentanones has been achieved, and for other less active substrates, cyclization occurs at lower temperatures with significantly reduced reaction times.

The synthesis of **2** follows Scheme 1 beginning with the preparation of IrBr(CO)((*R*)-(+)-BINAP) (**3**) by the addition of partially dissolved (*R*)-(+)-BINAP in toluene to a solution of (Bu₄N)[IrBr₂(CO)₂]. Equimolar addition of bromine to a solution of **3** in methylene chloride at room temperature results in the formation of a 1:1 mixture of facial (**4**) and meridional (**5**) isomers of IrBr₃(CO)((*R*)-(+)-BINAP) in up to 99% purified yield. Consecutive addition of two equivalents of diethyl isopropylidene malonate (DIM) and silver hexafluoroantimonate to a solution of **4** and/or **5** in methylene chloride under minimal light conditions leads to the formation of two isomers of **2** in up to 96% yield (Scheme 1). ³¹P{¹H} NMR spectroscopy identifies the isomers through two pairs of doublets, the first of which is seen at δ -15.2 and -19.7 with ²J_{PP} = 14.1 Hz and the second at δ -23.5 and -29.8 with ²J_{PP} = 19.6 Hz. While the facial isomer **4** affords only one isomer of **2**, the meridional isomer **5** yields both. The presence of DIM and (*R*)-(+)-BINAP was confirmed by ¹H NMR spectroscopy. In addition, the dicationic nature of **2** was evidenced by bromide addition to a 1:1 mixture of **2a** and **2b** with tetrabutylammonium bromide in dichloromethane-*d*₂ to reform **4**, as observed by ³¹P{¹H} NMR spectroscopy.

Initial catalytic experiments using **2** centered on the electrocyclicization of phosphonate aryl enone **6**, followed by a comparison of the catalytic activity of **2** to the most effective catalysts known for each substrate type (Table 1). Previous studies related to substituent effects on polarized aryl enones had revealed that Cu(ClO₄)₂ was an effective catalyst for cyclizations of activated aromatics such as **6**,[5] while Sc(OTf)₃ + stoichiometric LiClO₄ was an active promoter for the cyclization of polarized heteroaryl vinyl ketones.[6]

While the cyclization of **6** with Cu(ClO₄)₂ required 24 h at 80 °C,[5] the formation of **7** catalyzed by **2** proceeds even at room temperature, albeit slowly. Both of the Ir(III) complexes, **1** and **2**, provide full conversion (>99 %) of **6** to **7** at 40 °C in 12 h. However, a

dramatic reduction in the reaction time using **2** is observed when AgSbF₆ (10 mol % with respect to **6**) is added to the reaction mixture. The cyclization of **6** is complete in just 6 h at 40 °C, with concurrent precipitation of AgBr. The observation of AgBr formation indicates removal of the bromide ligand from **2** to form an Ir(III) trication *in situ*. While isolation of this active metal species has not been possible to date, the addition of AgSbF₆ indicates a viable approach to utilizing the high electrophilicity of tricationic complexes with non-coordinating anions. In sharp contrast to the results with **2**, addition of AgSbF₆ to the reaction of **6** with **1** does *not* generate any precipitate or lead to enhancement of the reaction rate. Only 64% conversion was obtained with **1** at 6 h with completion attained in 12 h. This observation is consistent with the fact that **1** has a Me group and not Br[−] as its sole anionic ligand. While AgSbF₆ clearly functions to enhance the catalytic activity of **2**, a control containing only AgSbF₆ yielded *no* cyclization catalysis. Based on these observations, complex **2** with AgSbF₆ as an additive proves to be an impressively effective catalyst system, yielding enhanced rates under mild conditions.

With this highly active catalyst in hand, electrocyclizations of several weakly polarized aryl enones were examined (Table 1). These substrates contain -CO₂Me, -PO(OEt)₂, -CN, and -NO₂ groups as electron-withdrawing substituents, and activated aromatics and heteroaromatics as electron-rich substituents. Functionalized cyclopentanones are obtained with **2** + AgSbF₆ under relatively mild conditions with high conversion (>99 %) and good yields. Comparison of catalysts for these aryl enones confirms that the use of **2** + AgSbF₆ allows substrate activation at lower temperatures and enhances rates relative to Cu(ClO₄)₂, Sc(OTf)₃ + LiClO₄, and **1**. As observed before, precipitation of AgBr is characteristic of cyclizations with **2** + AgSbF₆.

Consistent with the electronic properties of the nucleophilic component of the polarized Nazarov substrate, **8** is less reactive than **6** and cyclizes within 10 h using **2** + AgSbF₆ at 60 °C instead of 40 °C employed for **6** (entry 2). Cyclization of **8** using **1** as catalyst at 60 °C is much slower than with **2** + AgSbF₆, and with Cu(ClO₄)₂, only 50% conversion is obtained in 18 h. For the 3-substituted pyrrole substrate **10**, cyclization was reported to occur with Sc(OTf)₃ + LiClO₄ at 80 °C in 1.25 h.[6] In contrast, the iridium catalysts **2** + AgSbF₆ or **1** leads to complete conversion of **10** even at room temperature within 20 h (entry 3). While reactions of the less reactive pyrrole substrate **12** using Sc(OTf)₃, Sc(OTf)₃ + LiClO₄, and In(OTf)₃ + LiClO₄ stalled even at 80 °C, full conversion was obtained in 2 h using **1** (entry 4). This same cyclization needed only 50 min with **2** alone, and with AgSbF₆ added, the reaction time decreased further to only 20 min. The structure of the cyclobutyl product **13** was confirmed by X-ray crystallography (see CCDC 760899 for supplementary crystallographic data).

With **2** or **2** + AgSbF₆ as the catalyst, cyclization of the cyano aryl enone **14** to form **15** is obtained at 40 °C after 60 h (entry 5). While aryl enone **16** does not cyclize using **2** alone, the desired cyclization is promoted with **2** + AgSbF₆ at 80 °C (entry 6). It is worth noting that Cu(ClO₄)₂,[5] AgSbF₆, and **1** are all ineffective for cyclization of **14** and **16**, as is **2** or **2** + AgSbF₆ for **16** at temperatures up to 60 °C. Similarly, nitro aryl enone **18** could not be cyclized with Cu(ClO₄)₂,[5] yet **19** is obtained in the presence of **2** + AgSbF₆ at 60 °C in 36 h (entry 7). The formation of **19** was confirmed by ¹H NMR spectroscopy and high resolution mass spectrometry although it decomposed under all isolation conditions. Entries 5, 6, and 7 are the first examples of Nazarov cyclizations of polarized aryl enones with -CN and -NO₂ groups. Similarly, furyl cyclopentanone **21** can be obtained only with **2** + AgSbF₆ at 80 °C within 2 h (entry 8). The reaction with **1** leads to <35% conversion in 72 h and Sc(OTf)₃ + LiClO₄ cannot promote this cyclization.

Importantly, catalyst **2** does not decompose upon prolonged heating at 80 °C, in contrast to **1**, which is unstable at temperatures well above 45 °C.[18] In terms of catalyst synthesis, **2** avoids the triflate exchange step described for synthesizing **1**[13] and is thus a more accessible, as well as more reactive, catalyst. Despite the presence of the chiral BINAP in **2**, significant asymmetric induction has not been achieved (ee's of <15%).

In summary, we have designed a new, unusually electrophilic Ir(III) complex **2** and have shown that its use with one equivalent of AgSbF₆ generates the most reactive catalyst system for Nazarov cyclization of polarized substrates. The system, which generates a *tricationic* complex with non-coordinating anions *in situ*, surpasses the activity of the previously reported dication **1** and outperforms other catalysts for polarized Nazarov cyclization. This new catalyst system will allow access to unusually fused aromatic and heteroaromatic ring systems that can be functionalized into biologically active natural products and pharmaceuticals.

Experimental Section

Representative catalytic reaction: Aryl enone **12** (0.0197 g, 0.0845 mmol), **2** (0.0142 g, 0.00845 mmol), AgSbF₆ (0.00290 g, 0.00845 mmol) in CD₃NO₂ (0.7 mL) were reacted at 80 °C for 20 min to afford **13** (0.0139 g, 0.00596 mmol) in a 71% yield after flash column chromatography. Experimental details and spectroscopic information for preparation of all compounds are included in the Supporting Information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

Synthesis of $[\text{IrBr}(\text{CO})(\text{DIM})((R)\text{-}(+)\text{-BINAP})](\text{SbF}_6)_2$ (**2**)

Reaction conditions: [a] Br_2 (1 equiv.), rt, 15 min, CH_2Cl_2 [b] AgSbF_6 (2 equiv.), DIM (2 equiv.), CH_2Cl_2 , rt, 3 h, minimal light conditions. DIM = diethylisopropylidene malonate

Table 1

Cyclizations of various polarized aryl enones^a

entry	aryl enone	product	catalyst	temp (°C)	time (h)	conversion ^[b] (%)	yield ^[c] (%)
1			2 + AgSbF ₆	40	6	>99	77
			1	40	12	>99	68
			Cu(ClO ₄) ₂	40	6	20	-
2			2 + AgSbF ₆	60	10	>99	97
			1	60	18	>99	80
			Cu(ClO ₄) ₂	60	18	50	-
3			2 + AgSbF ₆	23	20	>99	80
			1	23	20	>99	62
			Sc(OTf) ₃ + LiClO ₄ [6]	80	1.25	nd ^[d]	68

entry	aryl enone	product	catalyst	temp (°C)	time (h)	conversion ^[b] (%)	yield ^[c] (%)
4			2 + AgSbF ₆ 1 Sc(OTf) ₃ + LiClO ₄	80 80 80	0.33 2 2	>99 >99 75 ^[e]	71 70 61
5			2 + AgSbF ₆ 1 Cu(ClO ₄) ₂	40 40 80	60 60 12	>99 100 ^[f] 100 ^[f]	60 - -
6			2 + AgSbF ₆ 1 Cu(ClO ₄) ₂	80 80 80	20.5 48 24	>99 100 ^[f] 100 ^[f]	59 - -

entry	aryl enone	product	catalyst	temp (°C)	time (h)	conversion (%)	yield (%)
	2 + AgSbF ₆ [c] 1 Cu(ClO ₄) ₂ [5]	60 60 80	36 36 72	>99 [f] [f]	99 [b] - -

entry	aryl enone	product	catalyst	temp (°C)	time (h)	conversion ^[b] (%)	yield ^[c] (%)
	2 + AgSbF ₆	80	2	>99	71
			1	80	>72	<35	-
			Sc(OTf) ₃ + LiClO ₄	80	2	[f]	-

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^[a] Reaction conditions: **2** (10 mol %), **2**AgSbF₆ = 1:1, CD₂Cl₂ or CD₃NO₂, minimal light.

^[b] Reactions were monitored and percent values were determined using ¹H NMR spectroscopy.

^[c] Isolated yields.

^[d] ¹H NMR = not determined, monitored by thin layer chromatography.

^[e] Conversion calculated based on recovered starting material.

^[f] No product detected.

^[g] AgSbF₆ (50 mol% with respect to **18**). No catalysis was observed in CD₂Cl₂ or with AgSbF₆ alone. TIPS = triisopropylsilyl.