Iridium Catalysis

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

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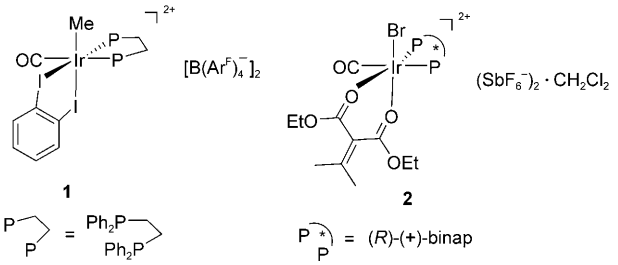
Since the discovery of the silicon-directed approach by Denmark and Jones,[1] the Nazarov reaction has been employed in the syntheses of a substantial number of natural products and bioactive molecules that contain highly functionalized five-membered carbocycles.[2] Originally, stoichiometric or super-stoichiometric amounts of Brønsted or Lewis acids were required to promote the Nazarov cyclization of divinyl ketones and aryl vinyl ketones (aryl enones), to generate cyclopentanones through a stereospecific 4π electrocyclization reaction.[3] The efficacy of the 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 $Cu(OTf)_2$,[4b,5] $Sc(OTf)_3$,[6] $[PdCl_2(MeCN)_2]$,[7] or $Cu(SbF_6)_2$[8] as a promoter. While moderate levels of asymmetric induction were achieved using [Sc(pybox)(OTf)$_3$][9] (pybox = pyridine bisoxazoline) and [Cu(pybox)(OTf)$_2$],[10] [Ni(bis{(*R*)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethyl}cyclohexylphosphine)-(thf)]$(ClO_4)_2$ offered notable enantioselectivity, but slow cyclization rates.[11]

Cationic complexes of heavier platinum group metals have been extensively studied for electrophilicly driven transformations.[12] In this context, Albeitz et al. reported the electrophilic complex [Ir(dppe)(CH_3)(CO)(dib)]$(BAr^F)_2$ (**1**), (dppe = 1,2-bis(diphenylphosphino)ethane, dib = 1,2-diiodobenzene, BAr^F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate), which promotes olefin polymerization by a cationic mechanism.[13] Subsequently, **1** was found to catalyze the Nazarov cyclization[14] and a tandem Nazarov/Michael addition sequence[15] with significantly higher reaction rates and at lower temperatures, when compared to other Lewis acid catalysts.

Despite these successes with the highly active complex **1**, the cyclization of aromatic substrates that contained cyano or nitro groups was not successful, and the catalysis of substrates that contained $PO(OEt)_2$ or *para*-tolylsulfonyl substituents was not efficient.[5] To obtain unusually functionalized cyclopentanones that are fused with aromatic or heteroaromatic residues, these limitations in scope represented a challenge that needed to be addressed. Such cyclization reactions represent powerful strategies for the syntheses of complex molecules and natural products, such as roseophilin[16] and the tetrapetalone family.[17] To increase the electrophilicity of the catalyst, a trication that was generated by Br^- abstraction was envisioned. This trication would be stabilized against decomposition by the bulkier diphosphine ligand, binap (2,2′-bis(diphenylphosphino)-1,1′-binaphthylene).



Herein, we describe the synthesis and reactivity of [IrBr(CO)(dim){(*R*)-(+)-binap}]$(SbF_6)_2$•CH_2Cl_2 (**2**), (dim = diethylisopropylidene malonate), a new catalyst that exhibits truly notable activity in these cyclization reactions. Extraction of the Br^- ligand in **2** in conjunction with the lability of the dim ligand opens a new route to generate extremely electrophilic d^6 iridium species for the electrocyclization of aryl enones that cannot be activated otherwise. Using catalyst **2**, the cyclization reaction of these unreactive substrates to afford the desired cyclopentanones has been achieved, and for other less active substrates, cyclization occurs at lower temperatures with significantly shorter reaction times.

The synthesis of **2** (Scheme 1) began with the preparation of [IrBr(CO){(*R*)-(+)-binap}] (**3**) from the addition of partially dissolved (*R*)-(+)-binap in toluene to a solution of $[IrBr_2(CO)_2](Bu_4N)$. Equimolar addition of bromine to a solution of **3** in dichloromethane at room temperature resulted in the formation of a 1:1 mixture of facial (**4**) and meridional (**5**) isomers of [$IrBr_3$(CO){(*R*)-(+)-binap}] in up to 99% yield of the purified product. Consecutive addition of two equivalents of diethylisopropylidene malonate (dim) and silver hexafluoroantimonate to a solution of **4** and/or **5** in dichloromethane under minimal light conditions led to the formation of two isomers of **2** in up to 96% yield (Scheme 1). $^{31}P\{^1H\}$ NMR spectroscopy identified the isomers through two

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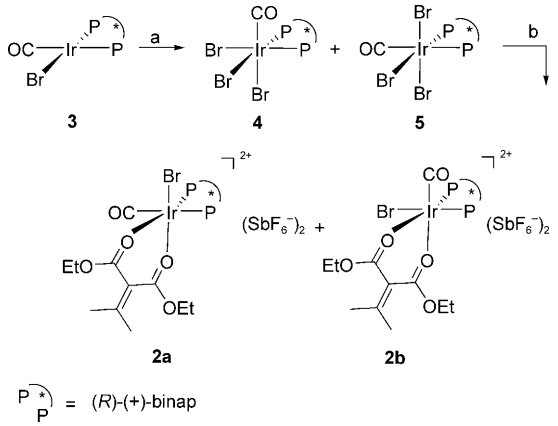


Scheme 1. Synthesis of [IrBr(CO)(dim)((*R*)-(+)-binap)]$(SbF_6)_2$ (**2**). Reaction conditions: [a] Br_2 (1 equiv), RT, 15 min, CH_2Cl_2 [b] $AgSbF_6$ (2 equiv), dim (2 equiv), CH_2Cl_2, RT, 3 h, minimal light conditions.

pairs of doublets, the first of which was observed at $\delta = -15.2$ and -19.7 ppm ($^2J_{PP} = 14.1$ Hz) and the second at $\delta = -23.5$ and -29.8 ppm ($^2J_{PP} = 19.6$ Hz). While facial isomer **4** afforded only one isomer of **2**, the meridional isomer **5** yielded a mixture of both. The presence of dim and (*R*)-(+)-binap was confirmed by ^1H NMR spectroscopy. Furthermore, the dicationic nature of **2** was made evident from the reformation of **4** following bromide addition to a 1:1 mixture of **2a** and **2b** (tetrabutylammonium bromide in [D_2]dichloromethane), as observed by $^{31}P\{^1H\}$ NMR spectroscopy.

Initial experiments using catalyst **2** focused on the electrocyclization of phosphonate aryl enone **6**, followed by a comparison of the catalytic activity of **2** to the most effective catalysts that are known for each substrate type (Table 1). Previous investigations into the substituent effects on the reactivity of polarized aryl enones revealed that $Cu(ClO_4)_2$ was an effective catalyst for the cyclization reactions of activated aromatic compounds, such as **6**,[5] while $Sc(OTf)_3$/stoichiometric $LiClO_4$ was an active promoter for the cyclization of polarized heteroaryl vinyl ketones.[6]

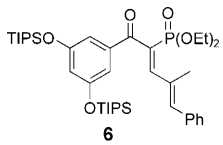
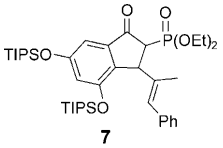
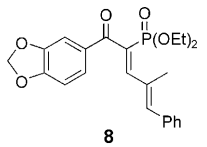
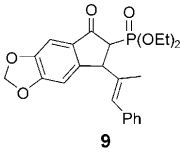
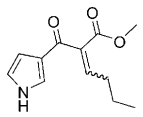
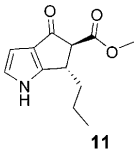
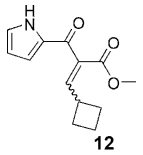
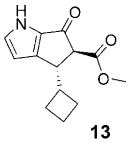
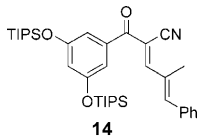
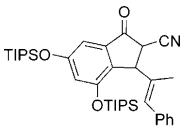
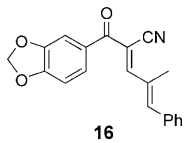
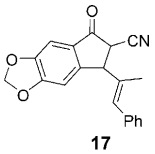
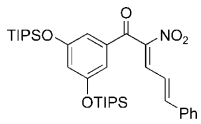
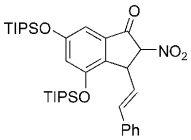
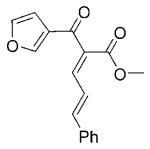
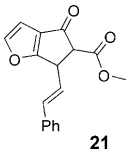
While the cyclization of **6** with $Cu(ClO_4)_2$ required heating for 24 hours at 80 °C,[5] the formation of **7** catalyzed by **2** proceeded even at room temperature, albeit slowly. Both of the Ir^{III} complexes, **1** and **2**, catalyzed complete conversion (>99 %) of **6** into **7** at 40 °C in 12 hours. However, a dramatic shortening of the reaction time of the **2**-catalyzed system was observed when $AgSbF_6$ (10 mol % with respect to **6**) was added to the reaction mixture. The cyclization reaction of **6** was complete in just 6 hours 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 the isolation of this active metal species has not been possible to date, the addition of $AgSbF_6$ is a viable approach to utilizing the high electrophilicity of tricationic complexes with noncoordinating anions. In sharp contrast to the results obtained with catalyst **2**, addition of $AgSbF_6$ to the reaction of **6** with **1** did not generate any precipitate or lead to an enhancement of the reaction rate. Only 64 % conversion was obtained with catalyst **1** at 6 hours, with completion attained in 12 hours. This observation is consistent with the fact that **1** has a methyl group, and not Br^-, as its sole anionic ligand. While $AgSbF_6$ clearly functions to enhance the catalytic activity of **2**, a control reaction that contained only $AgSbF_6$ yielded no cyclization catalysis. Based on these observations, complex **2** plus the $AgSbF_6$ additive was an impressively effective catalyst system, yielding enhanced rates under mild conditions.

With this highly active catalyst in hand, the electrocyclization reactions of several weakly polarized aryl enones were examined (Table 1). These substrates contain CO_2Me, $PO(OEt)_2$, CN, or NO_2 groups as electron-withdrawing substituents, and activated aromatic or heteroaromatic moieties as electron-rich substituents. Functionalized cyclopentanones were obtained using **2**/$AgSbF_6$ under relatively mild conditions with high conversion (>99 %) and good yields. Comparison of catalysts in the aryl enone cyclization reaction confirmed that the use of **2**/$AgSbF_6$ allowed substrate activation at lower temperatures and enhanced the rate of reaction more than $Cu(ClO_4)_2$, $Sc(OTf)_3/LiClO_4$, or **1**. As observed above, precipitation of AgBr is characteristic of cyclization reactions with **2**/$AgSbF_6$.

Consistent with the electronic properties of the nucleophilic component of the polarized Nazarov substrate, **8** is less reactive than **6** and cyclizes within 10 hours using **2**/$AgSbF_6$ at 60 °C instead of the 40 °C required for **6** (Table 1, entry 2). Cyclization of **8** using catalyst **1** at 60 °C is much slower than using **2**/$AgSbF_6$, and with $Cu(ClO_4)_2$, only 50 % conversion is obtained in 18 hours. For the 3-substituted pyrrole substrate **10**, cyclization was reported to occur with $Sc(OTf)_3/LiClO_4$ at 80 °C in 75 minutes.[6] In contrast, iridium catalysts **2**/$AgSbF_6$ and **1** both afforded complete conversion of **10** even at room temperature within 20 hours (entry 3). While reactions of the less-reactive pyrrole substrate **12** using $Sc(OTf)_3$, $Sc(OTf)_3/LiClO_4$, and $In(OTf)_3/LiClO_4$ stalled even at 80 °C, full conversion was obtained in 2 hours using **1** (entry 4). This same cyclization reaction was completed in only 50 minutes with **2** alone, and in the presence of the $AgSbF_6$ additive the reaction time decreased further to only 20 minutes. The structure of the cyclobutyl product **13** was confirmed by X-ray crystallography.[19]

In the presence of catalyst **2** or **2**/$AgSbF_6$, the cyclization of the cyanoaryl enone **14** to form **15** was obtained at 40 °C after 60 hours (Table 1, entry 5). While aryl enone **16** did not cyclize using **2** alone, the desired cyclization was accomplished using **2**/$AgSbF_6$ at 80 °C (entry 6). It is worth noting that $Cu(ClO_4)_2$,[5] $AgSbF_6$, and **1** were all ineffective for the cyclization reactions of **14** and **16**, as was **2** or **2**/$AgSbF_6$ for **16** at temperatures up to 60 °C. Similarly, nitroaryl enone **18** could not be cyclized with $Cu(ClO_4)_2$,[5] yet **19** is obtained in the presence of **2**/$AgSbF_6$ at 60 °C in 36 hours (entry 7). The formation of **19** was confirmed by ^1H NMR spectroscopy and high-resolution mass spectrometry although the sample decomposed under all isolation conditions. Table 1, entries 5, 6, and 7 show the first examples of the Nazarov cyclization reaction of polarized aryl enones with cyano and nitro groups. Similarly, furyl cyclopentanone **21** was obtained only with **2**/$AgSbF_6$ at 80 °C within 2 hours (entry 8). The reaction with **1**

Table 1: Cyclizations of various polarized aryl enones.[a]

Entry	Aryl enone	Product	Catalyst	*T* [°C]	*t* [h]	Conversion[b] [%]	Yield[c] [%]
1	 **6**	 **7**	**2**/$AgSbF_6$	40	6	>99	76
			1	40	12	>99	68
			$Cu(ClO_4)_2$	40	6	20	–
2	 **8**	 **9**	**2**/$AgSbF_6$	60	10	>99	97
			1	60	18	>99	80
			$Cu(ClO_4)_2$	60	18	50	–
3	 **10**	 **11**	**2**/$AgSbF_6$	23	20	>99	80
			1	23	20	>99	62
			$Sc(OTf)_3/LiClO_4$[6]	80	1.25	nd[d]	68
4	 **12**	 **13**	**2**/$AgSbF_6$	80	0.33	>99	71
			1	80	2	>99	70
			$Sc(OTf)_3/LiClO_4$	80	2	75[e]	61
5	 **14**	 **15**	**2**/$AgSbF_6$	40	60	>99	60
			1	40	60	–[f]	–
			$Cu(ClO_4)_2$	80	12	–[f]	–
6	 **16**	 **17**	**2**/$AgSbF_6$	80	20.5	>99	59
			1	80	48	–[f]	–
			$Cu(ClO_4)_2$	80	24	–[f]	–
7	 **18**	 **19**	**2**/$AgSbF_6$[g]	60	36	>99	99[b]
			1	60	36	–[f]	–
			$Cu(ClO_4)_2$[5]	80	72	–[f]	–
8	 **20**	 **21**	**2**/$AgSbF_6$	80	2	>99	71
			1	80	>72	<35	–
			$Sc(OTf)_3/LiClO_4$	80	2	–[f]	–

[a] Reaction conditions: **2** (10 mol%), **2**:$AgSbF_6$ = 1:1, CD_2Cl_2 or CD_3NO_2, minimal light. [b] Reactions were monitored by and conversion percentage values were determined using ^1H NMR spectroscopy. [c] Yield of isolated product. [d] nd = not determined; monitored by thin-layer chromatography. [e] Conversion calculated based on recovered starting material. [f] No product detected. [g] $AgSbF_6$ (50 mol% with respect to **18**). No catalysis was observed in CD_2Cl_2 or with $AgSbF_6$ alone. TIPS = triisopropylsilyl.

gave <35% conversion in 72 hours and $Sc(OTf)_3/LiClO_4$ did not promote this cyclization.

Importantly, catalyst **2** does not decompose upon prolonged heating at 80°C, in contrast to **1**, which is unstable at temperatures above 45°C.[18] In terms of the synthesis of the catalysts, the synthesis of **2** avoids the triflate exchange step in the synthesis of **1**[13] and is thus a more accessible, as well as a more reactive, catalyst. Despite the presence of chiral binap in

2, significant asymmetric induction has not yet been achieved (*ee* values of less than 15%).

In summary, we have designed a new, unusually electrophilic Ir^{III} complex **2** and have shown that its use with one equivalent of $AgSbF_6$ generates the most reactive catalyst system for Nazarov cyclization of polarized substrates. The system, which generates a tricationic complex with noncoordinating anions in situ, surpasses the activity of the previously reported dication **1** and outperforms other catalysts for the polarized Nazarov cyclization reaction. 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: A solution of aryl enone **12** (0.0197 g, 0.0845 mmol), **2** (0.0142 g, 0.00845 mmol), and $AgSbF_6$ (0.00290 g, 0.00845 mmol) in CD_3NO_2 (0.7 mL) was heated at 80 °C for 20 minutes to afford **13** (0.0139 g, 0.00596 mmol) in 71% yield after column chromatography on silica gel. Experimental details and spectroscopic information for the preparation of all compounds are included in the Supporting Information.

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[19] CCDC 760899 (**13**) contains the supplementary crystallographic information for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

