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Asymmetric Nazarov Cyclizations Catalyzed by Chiral-at-Metal Complexes

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Abstract. The application of Lewis acidic chiral-at-metal complexes of iridium(III) and rhodium(III) as catalysts for the asymmetric polarized Nazarov cyclization of dihydropyran- and indole-functionalized α-unsaturated β-ketoesters is reported (overall 24 examples). For both substrate classes, catalyst loadings of 2 mol% were found to be sufficient for achieving high yields and high stereoselectivities. The cyclized dihydropyran products were isolated in 85–98% yield, with 89%–>99% ee, and *trans*/*cis* ratios of 15:1–50:1 (9 examples). The cyclized indole products were typically isolated in more than 70% yield and in up to 93% yield, typically with more than 90% ee and in up to 97% ee, and *trans*/*cis* ratios of 12:1–28:1 (15 examples).

Keywords: Nazarov cyclization; chiral Lewis acid; asymmetric catalysis; chiral-at-metal; iridium; rhodium.

The Nazarov cyclization represents a powerful method to generate five-membered carbocycles, namely highly substituted cyclopentenones, which are a frequently occurring structural motif in natural products and bioactive compounds and their precursors.[1-3] In recent years, significant efforts have been devoted to the development of catalytic methods for asymmetric Nazarov cyclizations.[4] Typically, either a chiral Brønsted acid or a chiral Lewis acid (LA) coordinates to a divinyl ketone or aryl vinyl ketone substrate and triggers a conrotatory 4π-electrocyclization of an intermediate pentadienyl cation, which is followed by a deprotonation / reprotonation sequence to provide the final chiral cyclopentenone (Figure 1, A).[5-19] The asymmetric induction in this process takes place during the key electrocyclization step or during the final reprotonation step.[7,10,18b,19] With respect to chiral Lewis acidic catalysts, chiral bis-oxazoline,[6,8,14,16] pyridine-2,6-bisoxazoline,[5-7,10,12] and tris-oxazoline[11] complexes of copper(II),[6,8,11,14,16] but also of other metals, such as scandium(III),[5,7,10] iron(II),[12] and cobalt(III),[12] have been among the most popular ones for asymmetric Nazarov cyclizations. Furthermore, nickel(II) phosphine,[9] chromium(III) salen,[13] palladium(0) phosphoramidite,[15] and nickel(II) bisimino-bisquinoline[17] complexes have been reported as chiral catalysts for asymmetric Nazarov cyclizations. However, with regard to asymmetric Nazarov cyclizations, the combination of low catalyst loadings, high enantioselectivities, high diastereoselectivities, and high yields is still a formidable challenge, even for favorably activated substrates.

Relevant to this study, Frontier and Eisenberg reported highly reactive dicationic constitutionally and configurationally well-defined iridium(III) complexes for catalyzing a polar Nazarov cyclization[20] and a tandem Nazarov/Michael addition sequence[21] with impressive reaction rates although the products were formed racemic. The high catalytic activity was traced back to the unusual electrophilicity of the iridium(III) complexes combined with a two-point activation of the substrates at two adjacent coordination sites of the iridium(III) catalyst.

We recently introduced hexacoordinated, octahedral iridium(III) and rhodium(III) complexes bearing two cyclometalated 5-*tert*-butyl-2-phenylbenzoxazoles or the analogous benzothiazole ligands in addition to two exchange-labile acetonitriles as a new class of asymmetric catalysts (Figure 1, B).[22] With all ligands being achiral, chirality is induced upon the asymmetric assembly of the cyclometalated ligands around the stereogenic metal center. This arrangement is configurationally stable, providing either a left-handed (Λ-configuration) or a right-handed (Δ-configuration) propeller, which is responsible for the asymmetric induction.[23] Over the past few years, we[22] and others[24,25] have demonstrated the versatility of this class of catalysts for a variety of asymmetric reactions. However, in the majority of the so far

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reported applications, *N*,*O*-bidentate coordinating substrates were employed, particularly 2-acylimidazoles, *N*-acylpyrazoles, and 2 acylpyridines.[26] Herein, we now demonstrate that these bis-cyclometalated iridium(III) and rhodium(III) complexes are also excellent catalysts for the asymmetric Nazarov cyclization of dihydropyran- (**1**) and indole-functionalized (**3**) α-unsaturated β-ketoesters, which are supposed to be activated via *O*,*O*-bidentate coordination. With catalyst loadings of merely 2 mol%, high yields and high stereoselectivities were achieved (Figure 1, B).

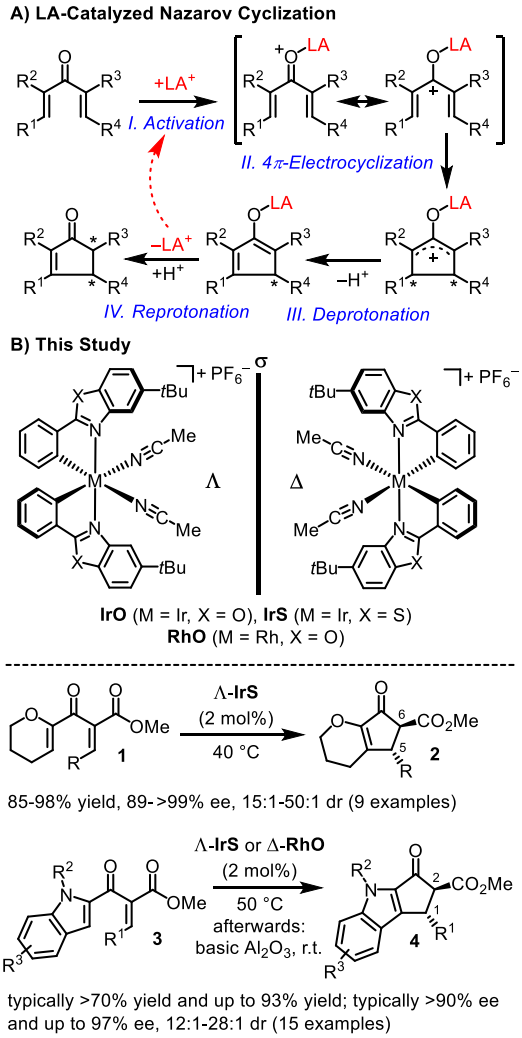
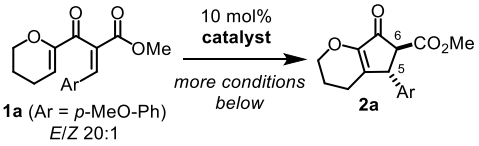


Figure 1. A) General mechanism of Lewis-acid-catalyzed Nazarov cyclizations. B) Lewis-acid-catalyzed Nazarov cyclizations with chiral-at-metal complexes **IrO**, **IrS**, and **RhO**, which are presented in this work. LA = Lewis acid.

We wondered if our recently developed chiral-at-metal Lewis acids would be suitable catalysts for asymmetric Nazarov cyclizations of dienone substrates and therefore started with investigating the Nazarov cyclization of dihydropyran substrate **1a** (Table 1). To our delight, both bis-cyclometalated iridium(III) complexes Λ-**IrO**[27] (entry 1) and Λ-**IrS**[26,28] (entry 2) as well as bis-cyclometalated rhodium(III) complex Δ-**RhO**[29] (entry 3) provided desired cyclopentenone product **2a** with high enantioselectivities at 50 °C at catalyst loadings of 10 mol% (entries 1-3). Rhodium catalyst Δ-**RhO** was found to be slightly superior compared to iridium congeners Λ-**IrS** and Λ-**IrO** with respect to enantioselectivity and moreover was found to be superior in terms of catalytic activity, which allowed us to perform the reaction at room temperature (compare entries 4-6).

Table 1. Initial Experiments with Dihydropyran Substrate **1a**[a)]



Entry	Cat.	t (h)	T (°C)	Conv.[b)]	ee (%)[c)]
1	Λ-**IrO**	24	50	near complete	91 (5*R*,6*S*)
2	Λ-**IrS**	24	50	near complete	91 (5*R*,6*S*)
3	Δ-**RhO**	24	50	full	-93 (5*R*,6*S*)
4	Λ-**IrS**	44	r.t.	partial	n.d.[d)]
5	Λ-**IrO**	44	r.t.	partial	n.d.
6	Δ-**RhO**	12	r.t.	full	-93 (5*S*,6*R*)

[a)]Reaction conditions: Substrate **1a** (16.5 µmol) and the catalyst (1.65 µmol) in 1,2-dichloroethane at c = 0.05 M and at the indicated temperature. *E*/*Z* ratio of substrate **1a** of 20:1 determined by ^{1}H-NMR. [b)]Estimated by a combination of TLC and HPLC analysis. [c)]Determined from the crude product mixtures by HPLC analysis on chiral stationary phase; exclusively determined for the main trans diastereomer. [d)]n.d. = not determined.

Due to the satisfactory results obtained with **IrS** and in consideration of the easier synthesis and availability of **IrS** compared to **RhO**,[26,28,29] we decided to continue our study with catalyst Λ-**IrS** and screened for optimal reaction conditions. When we increased the concentration of substrate **1a** in 1,2-dichloroethane (DCE) from 0.05 M (Table 1) to 0.3 M (Table 2) and slightly reduced the temperature from 50 °C to 40 °C while maintaining a catalyst loading of 10 mol%, the enantioselectivity for **2a** increased from 91% ee to 93% ee (Table 2, entry 1). The addition of 10% (v/v) water did not change the outcome in terms of conversion and stereoselectivity (entry 2). Furthermore, the use of dry solvent and the execution under inert gas atmosphere had no effect on selectivity and yield (entry 3), which indicates that dry solvents are neither necessary nor beneficial. To our delight, we could decrease the catalyst loading from 10 mol% to 2 mol% without a drop in performance (entry 4). When we replaced solvent DCE with hexafluoro-2-isopropanol (HFIP), the enantioselectivity slightly declined but the reaction was significantly accelerated (entry 5). Eventually, a mixture of DCE and 1 equivalent of HFIP (with respect to substrate **1a**) was found to give virtually the same enantioselectivity as pure DCE but

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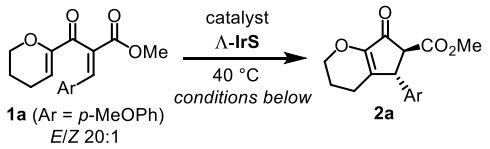
accelerated the reaction significantly and was hence selected as the solvent mixture of choice. Under these conditions, the reaction was completed within 7 h at 40 °C at a catalyst loading of 2 mol% Λ-**IrS**, and cyclopentenone product **2a** was provided with 93% ee with respect to the major *trans* diastereomer (entry 6). Other investigated solvents turned out to be less suitable (entries 7-14).

Table 2. Optimization of Reaction Conditions for Dihydropyran Substrate **1a** with Λ-**IrS** catalyst.[a)]



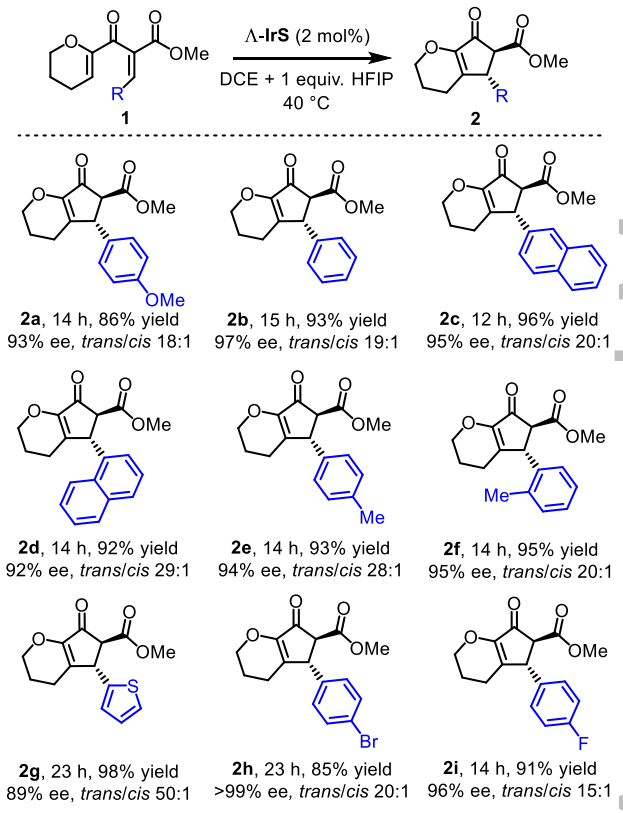
1a (Ar = *p*-MeOPh)
E/*Z* 20:1

2a

Entry	Λ-**IrS**	Solvent	t (h)	Conv.[b)]	ee (%)[c)]
1	10 mol%	DCE	13	full	93
2	10 mol%	DCE /10% H_2O	13	full	93
3	10 mol%	DCE	13	full	93
4	2 mol%	DCE	13	full	93
5	2 mol%	HFIP	7	full	90
6	**2 mol%**	**DCE/1 eq HFIP**	**7**	**full**	**93**
7	2 mol%	$CHCl_3$	14	ca. 95%	92
8	2 mol%	EtOAc	14	low	80
9	2 mol%	DME	14	low	30
10	2 mol%	MeCN	14	low	30
11	2 mol%	toluene	7	low	30
12	2 mol%	THF	7	low	20
13	2 mol%	MTBE	7	low	20
14	2 mol%	MeOH	14	low	3

[a)]Reaction conditions: Substrate **1a** (14.5–56.0 µmol) and Λ-**IrS** (0.70–1.45 µmol) in the indicated solvent at c = 0.3 M, at a temperature of 40 °C, and for the indicated time under standard atmosphere. *E*/*Z* ratio of substrate **1a** of 20:1 determined by ^{1}H-NMR. [b)]Reaction was performed under an inert gas atmosphere in a dry solvent. [c)]Estimated by a combination of TLC and HPLC analysis. [d)]Determined from crude product mixtures by HPLC analysis on chiral stationary phase; exclusively determined for the *trans* diastereomer.

With optimized reaction conditions in hand (Table 2, entry 6), we then investigated the scope for the dihydropyran-functionalized α-unsaturated β ketoesters (**1**; Scheme 1). For substrates with electronically neutral aromatic substituents R = Ph (product **2b**), R = 1-naphthyl (product **2c**), and R = 2-naphthyl (product **2d**), full conversion was found after reactions times of 12-15 h and products **2b**–**d** were isolated in yields of 92-96% with ee values ranging from 92-97% (ee values for the *trans* diastereomers) and dr values in the range of 19:1–29:1 (*trans*/*cis*). Substrates with electron-rich aromatic substituents *p*-MeO-Ph (product **2a**), *p*-Me-Ph (product **2e**), and *o*-Me-Ph (product **2f**) gave comparable results (86-95% yields; 93-95% ee (*trans* diastereomers); *trans*/*cis* 18:1-28:1; full conversion found for all three after 14 h). We also tested a substrate containing the heteroaromatic substituent R = thiophen-2-yl (product **2g**). In this case, full conversion was found after 23 h and the product was isolated in 98% yield with 89% ee (*trans* diastereomer) and a *trans*/*cis* ratio of 50:1. Finally, we investigated substrates with electron-deficient substituents R = *p*-Br-Ph (product **2h**) and R = *p*-F-Ph (product **2i**), which also gave good results (85% and 91% yield; >99% ee and 96% ee (*trans* diastereomers); *trans*/*cis* ratios of 20:1 and 15:1; full conversion after 23 h and 14 h).[11] It is important to note that for all reactions substrates were employed as *E*/*Z*-mixtures with *E*/*Z*-ratios ranging from 3:1 to >30:1 although the Nazarov cyclization products were obtained in all cases with high diastereo- and enantioselectivities. For example, product **2b** was obtained with 97% ee and 19:1 dr although the dienone substrate featured a low *E*/*Z*-ratio of just 3:1, thus demonstrating a stereoconvergent reaction. This can be traced back to well-established Lewis acid and transition metal catalyzed *E*/*Z*-isomerizations of the dienone substrates.[30-34]



Scheme 1. Scope for the Nazarov cyclization of dihydropyran-functionalized α-unsaturated β-ketoesters. Reaction conditions: *E*/*Z*-mixture of substrate **1** (1.0 equiv.; approx. 80-90 µmol) with catalyst Λ-**IrS** (2 mol%) in a mixture of DCE with 1.0 equiv. HFIP (1 equiv. with respect to substrate **1**) at c = 0.3 M in a rubber-sealed, screw-capped vial kept at 40 °C for the indicated time. *E*/*Z*-ratios of substrates were ranging from 3:1 to >30:1 (see SI for more details). Isolated yields provided. The dr values (*trans*/*cis*) were determined by ^{1}H NMR analysis of the crude product mixtures. The ee values were determined

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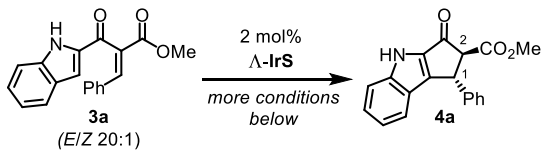
for the *trans* diastereomers from isolated products by HPLC analysis on chiral stationary phase.

Encouraged by these promising results with the dihydropyran-functionalized α-unsaturated β-ketoesters, we next decided to study indole-functionalized α-unsaturated β-ketoesters (**3**). The reaction conditions optimization for these substrates are shown in Table 3. Interestingly, compared to dihydropyran substrate **1a** (Table 2), the Λ-**IrS**-catalyzed Nazarov cyclization with indole substrate **3a** displayed a distinct solvent dependance (Table 3): DCE, as well as a variety of other common solvents, were found to be completely unsuitable for this reaction (entries 1-9). In contrast, a 1:1 mixture of DCE and HFIP provided desired cyclization product **4a** with 90% ee (entry 10; ee of the major trans diastereomer). Eventually, pure HFIP turned out to be the solvent of choice, which provided full conversion after 24 h at 50 °C and an enantioselectivity of 93% for product **4a** (entry 11).

Table 3. Optimization of Reaction Conditions for Indole Substrate **3a** with Λ-**IrS** as Catalyst.[a)]



3a (*E*/*Z* 20:1) → **4a**

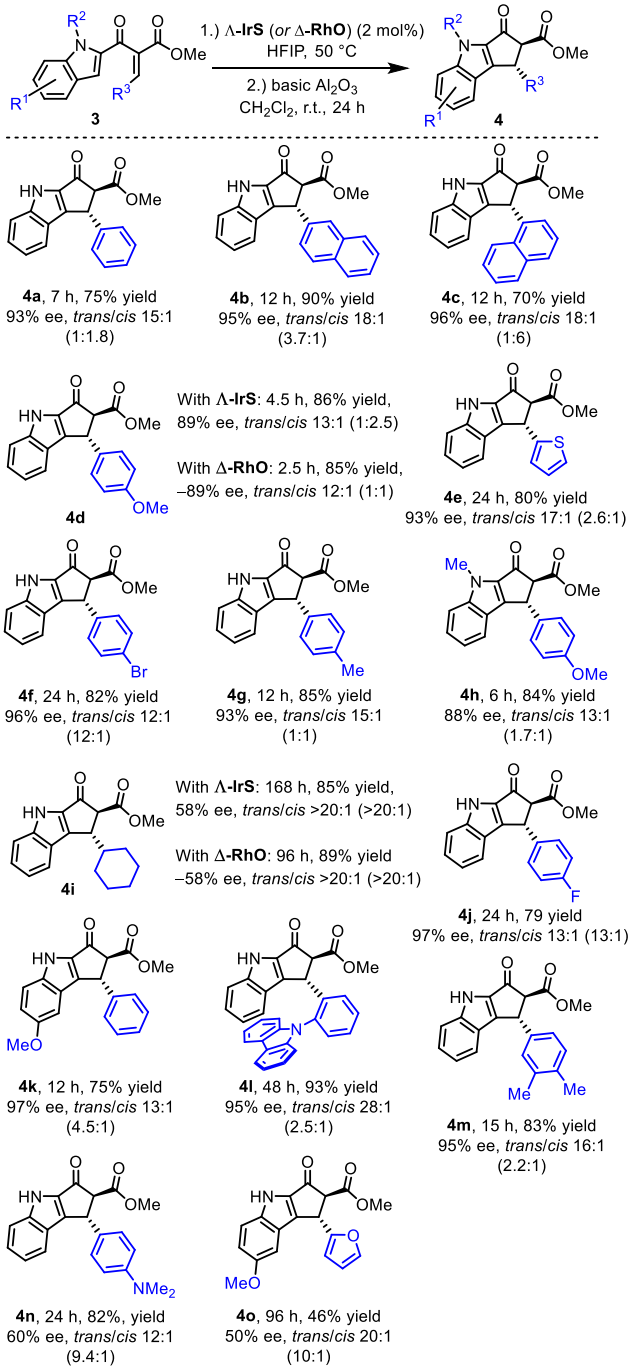
Entry	Solvent	T (°C)	Conv.	ee (%)
1	DCE	40	none	n.a.
2	DCE	50	trace	n.d.
3	$CHCl_3$	60	none	n.a.
4	$MeNO_2$	60	trace	n.d.
5	DMF	60	trace	n.d.
6	THF	60	none	n.a.
7	toluene	60	none	n.a.
8	EtOAc	60	trace	n.d.
9	dioxane	60	trace	n.d.
10	DCE/HFIP 1:1	50	ca. 95%	90 (1*R*,2*S*)
11	**HFIP**	**50**	**full**	**93 (1*R*,2*S*)**

[a)] Reaction conditions: Substrate **3a** (28.5 µmol) and Λ-**IrS** (0.6 µmol) in the indicated solvent at c = 0.3 M and at the indicated temperature for 24 h under standard atmosphere in a screw-capped vial. *E*/*Z* ratio of substrate **3a** of 20:1 was determined by ^{1}H-NMR. [b)]Estimated by a combination of TLC and HPLC analysis. [c)]Determined from crude product mixtures by HPLC analysis on chiral stationary phase; exclusively determined for the *trans* diastereomer. [d)]n.a. = not applicable. [e)]n.d. = not determined.

Notably, we observed during our experiments with indole substrate **3a** that the *cis* diastereomer product was initially predominant in the reaction mixture (kinetic product). In case of other indole-functionalized α-unsaturated β-ketoesters (**3**), we observed for short reaction times also at least initially low *trans*/*cis* ratios (Scheme 2). Such a *cis* selectivity for Nazarov cyclizations has been reported for iridium catalysts and binol phosphates as organocatalysts,[18a,20b] whereas other metal-based Lewis acid catalysts are commonly known for providing the trans product.[7,11,14] However, after prolonged reaction times with catalyst **IrS** (or **RhO**) the *trans* diastereomers became predominant (thermodynamic product). As the *trans*/*cis* equilibration was found to be very slow under the applied cyclization conditions, which led to partial decomposition of the products, we relied in case of all indole products (**4**) on a modified *trans*/*cis* equilibration protocol from Rueping and coworkers, which was applied after the actual cyclization:[18a] The crude cyclized indole products were dissolved in CH_2Cl_2 and simply stirred with basic aluminum oxide as weak insoluble base for 24 h at room temperature (details in the experimental section). With optimized reaction conditions (Table 3, entry 11) and the described trans/cis equilibration protocol in hands, we next investigated the scope for the indole-functionalized α-unsaturated β-ketoesters. The results of this scope screening are shown in Scheme 2.

For most of the indole-functionalized substrates, we obtained, apart from a few exceptions (products **4i**, **4n**, and **4o**), comparable results in terms of stereoselectivity (88-97% ee) compared to the dihydropyran-functionalized substrates. Moreover, the indole-functionalized products were, apart from one exception (product **4o**), obtained in good albeit slightly lower yields than the dihydropyran-functionalized products (70-93% yield). The observed dr values were, after the aluminum oxide induced *cis*/*trans* equilibration, in the same range as the dr values of the dihydropyran-substituted products (*trans*/*cis* 12:1-28:1). In terms of isolated yields, p-MeO-Ph substituted products **4d** and **4h**, 2-thiophenyl substituted product **4e**, *p*-Br-Ph substituted product **4f**, *p*-Me-Ph substituted product **4g**, *p*-F-Ph substituted product **4j**, *o*-(*N*-carbazolyl) Ph substituted product **4l**, 3,4-Me_2-Ph substituted product **4m**, and *p*-NMe_2-Ph substituted product **4n** were all obtained in >80% yield. Ph substituted products **4a** and **4k**, 2-naphthyl substituted product **4b**, and 1-naphthyl substituted product **4c** were obtained with yields in the range of 70–80%. In terms of selectivity, ee values of more than 95% were found for 1-naphthyl substituted product **4c**, *p*-Br-Ph substituted product **4f**, *p*-F-Ph substituted product **4j**, phenyl substituted product **4k**, and *o*-(*N*-carbazolyl) Ph substituted product **4l**. It is remarkable that the cyclization of sterically congested product **4l** worked so well. Enantioselectivities of 90–95% were found for Ph substituted **4a**, 2-naphthyl substituted **4b**, 2-thiophenyl substituted **4e**, *p*-Me-Ph substituted **4g** and 3,4-Me_2-Ph substituted **4m**. For *p*-MeO-Ph substituted **4d** and **4g**, ee values of 88% were found in both cases. Cyclohexyl substituted **4i** was obtained with modest 58% ee with both catalysts Λ-**IrS** and Δ-**RhO**, which is, however, a notable result for an alkylated Nazarov product in consideration of previous literature reports.[11,14] As expected, Δ-**RhO**

catalyzed this reaction faster than Λ-**IrS**: full conversion was reached after 170 h with Λ-**IrS** and after 98 h with Δ-**RhO**. Also, *p*-NMe_2-Ph substituted 4n was obtained with modest 60% ee. Finally, 2-furyl substituted **4o** was obtained in 46% yield with an ee of 50%. In this respect, it is noteworthy that we observed the formation of a considerable amount of side products in case of product **4o**, which we did not observe in case of all other products **4a-n**.[14]



Scheme 2. Scope for the Nazarov cyclization of indole-functionalized α-unsaturated β-ketoesters. Reaction conditions for step 1: *E*/*Z*-mixture of substrate **3** (1.0 equiv.; approx. 70−90 µmol) with catalyst Λ-**IrS** (or Δ-**RhO**; each 2 mol%) in HFIP at c = 0.3 M in a rubber-sealed, screw-capped vial kept at 50 °C for the indicated reaction time. *E*/*Z*-ratios of substrates were ranging from 7:1 to >30:1 (see SI for more details). Isolated yields provided. The dr values (*trans*/*cis*) were determined by ^{1}H NMR analysis of the crude product mixtures. Values in brackets are the dr values observed before Al_2O_3-induced equilibration. The ee values were determined for the trans diastereomers from isolated products by HPLC analysis on chiral stationary phase.

The proposed mechanism, which is based on published work on the mechanism of the Nazarov cyclization[1] and the established properties of our chiral-at-metal catalysts,[22] is shown in Figure 2. An *O*,*O*-bidentate coordination[20b] of the α-unsaturated β-ketoesters to the iridium- or rhodium-based Lewis acids (substrate/catalyst complex **A**) leads to an electronic activation (resonance structure **B**) and induces a conrotatory 4π-cyclization to afford a catalyst-bound cyclopentadienyl cation (**C**), in which the asymmetric induction is provided by the helical chirality of the bis-cyclometalated C_2-symmetrical Lewis acid. A subsequent deprotonation (**D**) and reprotonation generate the catalyst bound Nazarov product (**E**). Upon release of the product, a new catalytic cycle can be initiated. For the indole substrates, the kinetic product is the *cis* diastereomer, which then either slowly epimerizes to the thermodynamically more stable *trans* diastereomer under the reaction conditions or faster upon treatment with base. The benefit of hexafluoroisopropanol (HFIP) can be rationalized with its function as a weak acid which facilitates the release of the catalyst-bound product and thereby suppresses product inhibition.

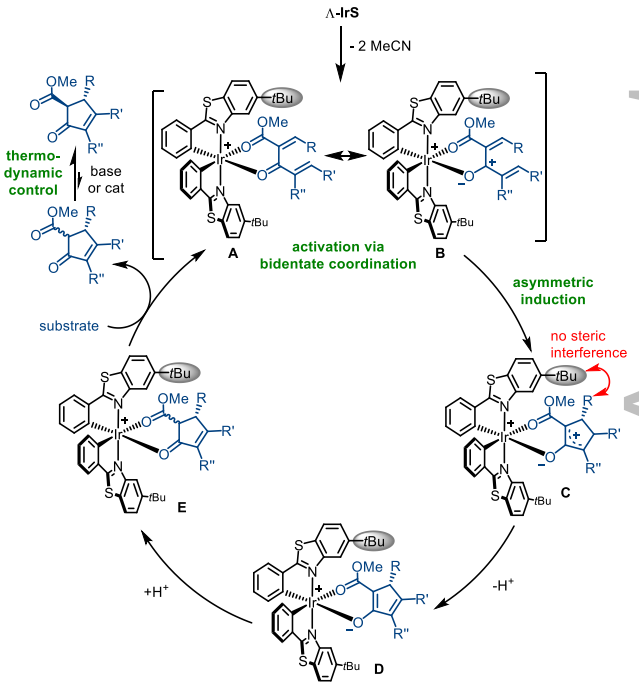


Figure 2. Proposed mechanism for the Nazarov cyclization including activation, asymmetric induction and diastereocontrol shown for Λ-**IrS**.

In summary, attractive key features of the here presented Nazarov cyclizations with chiral-at-metal catalyst **IrS** and for selected examples with **IrO** and **RhO** are 1.) the low catalyst loadings of just 2 mol%, 2.) no requirement for expensive counteranions such as $BArF^-$, NTf_2^- or SbF_6^-, 3.) dry solvents and inert gas atmosphere are neither required nor beneficial, and 4.) Nazarov cyclizations with two different substrates, namely dihydropyran- (**1**) and indole-functionalized (**3**) α-unsaturated β-ketoesters, were both performed with one single catalyst Λ-**IrS** in short reaction times and with satisfactory selectivities and yields.[11,14,17] Even though the presented method just requires 2 mol% of catalyst Λ-**IrS**, the reaction times for the dihydropyran substrates (**1**) remained < 24 h while providing excellent yields and enantio¬selectivities, even for more challenging products such as *p*-Br-Ph substituted **2h** and *p*-F-Ph substituted **2i** (Scheme 1). In contrast, 20 mol% of a copper(II) bis-oxazoline catalyst was required as recently reported by Tang and coworkers to provide **2h** and **2i** after > 24 h with comparable selectivities but lower yields (Tang et al.: 2h after 57 h with 76% yield and 96% ee; **2i** after 30 h with 69% yield and 96% ee).[11] Furthermore, we obtained with 2 mol% of catalyst Λ-**IrS** comparable yields and enantioselectivities as Rueping and coworkers with a recently reported copper(II) bis-oxazoline catalyst, which they usually employed in a loading of 5 mol%, for indole-functionalized Nazarov products **4**.[14] In this respect, it is also remarkable that sterically congested indole product **4l** could be obtained with just 2 mol% of Λ-**IrS** with excellent yield and high stereoselectivity (Scheme 2). Accordingly, the here reported Lewis acidic chiral-at-metal complexes may be employed as catalysts for challenging asymmetric Nazarov cyclizations.

In conclusion, we have applied chiral-at-metal iridium and rhodium catalysts to 24 different dienone Nazarov cyclization substrates, namely 9 dihydropyran-functionalized α-unsaturated β-ketoesters and 15 indole-functionalized α-unsaturated β-ketoesters. The majority of the desired Nazarov cyclization products were obtained in good to excellent yields and enantioselectivities as well as with satisfactory trans/cis ratios. Dry solvents and inert gas atmosphere are not required which allows a highly convenient reaction setup. Moreover, all 24 Nazarov cyclizations could be performed with a catalyst loading of just 2 mol% within < 24 h for all dihydropyran substrates and within ≤ 24 h with respect to the actual cyclization step for most of the indole substrates. These low catalyst loadings in combination with the inexpensive (achiral) ligands in the ligand sphere of the chiral iridium and rhodium catalysts should offset the higher cost for iridium and rhodium. Furthermore, although the requirement for a bidentate coordination of the substrate to the catalyst restricts the substrate scope to divinyl and aryl vinyl ketones with an additional coordinating ester group in β-position, the versatility of the ester group for further functional group interconversions in combination with the observed high stereoselectivities should render this method attractive for synthetic applications.

Experimental Section

Representative Nazarov cyclization for dihydropyran substrate: A vial (1.5 mL) was charged with an *E*/*Z*-mixture of dihydropyran-functionalized α-unsatured β-ketoester **1a** (25.2 mg, 83.5 µmol, 1.00 equiv.), catalyst Λ-**IrS** (1.6 mg, 1.7 µmol, 2 mol%), and a stock solution of DCE (280 µL) containing 1 equiv. of HFIP with respect to substrate **1a**. The vial was then tightly capped with a rubber-sealed screw cap, homogenized by sonication (1 min), and kept at 40 °C for 14 h after which TLC analysis indicated full conversion. The solvent was removed under reduced pressure and the dr value determined by ^{1}H NMR analysis of the crude product: *trans*/*cis* 18:1. Finally, the crude product was purified by flash chromatography (*n*-hexane/EtOAc 3:1) to give desired Nazarov cyclization product **2a** as a colorless viscous oil (21.7 mg, 71.8 µmol, 86%). Enantiomeric excess of the *trans* diastereomer of the isolated product determined by chiral HPLC analysis: 93% ee (Chiralpak AD-H column (5 µm; 25 cm x 4.6 mm), λ = 238 nm, *n*-hexane / isopropanol 70:30, 0.8 mL/min, column temp.: 25 °C; t_R (major) = 10.0 min, t_R (minor) = 12.8 min).

$[\alpha]_D^{27}$ = –228 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, CDCl3): δ = 7.05 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 6.87 (d, *J* = 8.6 Hz, 2H, H_{Ar}), 4.22–4.09 (m, 3H, H_{Aliph}), 3.79 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.29 (d, J = 2.2 Hz, 1H, C*H*) 2.28–2.07 (m, 2H, H^{Aliph}), 2.02–1.83 (m, 2H, H_{Aliph}) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.2, 169.0, 159.3, 149.8, 147.8, 131.9, 128.5, 114.7, 67.2, 59.6, 55.5, 52.9, 47.1, 22.4, 21.5 ppm; IR (ATR): $\tilde{\nu}$ = 2952 (w), 2929 (w), 2845 (w), 1739 (m), 1713 (s), 1648 (w), 1611 (w), 1511 (w), 1437 (w), 1400 (w), 1301 (w), 1249 (m), 1166 (w), 1121 (w), 1066 (w), 1032 (w), 978 (w), 915 (w), 836 (w), 567 (w) cm^{-1}; HRMS (ESI): *m*/*z* calcd. for $C_{17}H_{18}O_5Na_1$ $[M+Na]^+$: 325.1046; found: 325.1048.

Representative Nazarov-cyclization for indole substrate: A vial (1.5 mL) was charged with an *E*/*Z*-mixture of indole-functionalized α-unsatured β-ketoester **3a** (26.0 mg, 85.2 µmol, 1.00 equiv.), catalyst Λ-**IrS** (1.6 mg, 1.7 µmol, 2.0 mol%) and HFIP (280 µL). The vial was then tightly capped with a rubber-sealed screw cap, homogenized by sonication (1 min), and kept at 50 °C for 7 h after which TLC analysis indicated full conversion. The solvent was removed under reduced pressure and the dr of the crude product determined by ^{1}H NMR analysis: trans/cis 1:1.8. The crude product was then dissolved in CH_2Cl_2 (7 mL), basic Al_2O_3 powder (140 mg; Sigma Aldrich, 58 Å pore size, pH 9.5 ± 0.5 in water) added, and the mixture stirred at r.t. for 24 h. Next, the crude mixture was passed through a short plug of silica gel with EtOAc/MeOH (removal of the powdered Al_2O_3), the solvent removed under reduced pressure, and the dr of the crude, equilibrated product determined by ^{1}H NMR analysis: *trans*/*cis* 15:1. Finally, the crude product was purified by flash chromatography (*n*-hexane / EtOAc 3:1) to give desired Nazarov cyclization product **4a** as a colorless solid (19.4 mg, 63.5 µmol, 75%). Enantiomeric excess of the *trans* diastereomer of the isolated product determined by chiral HPLC analysis: 93% ee (Chiralpak

AD-H column (5 µm; 25 cm x 4.6 mm), λ = 254 nm, *n*-hexane / isopropanol 90:10, 0.6 mL/min, column temp.: 25 °C; t_R (major) = 23.0 min, t_R (minor) = 32.1 min).

$[\alpha]_D^{27}$ = –102 (c 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, CDCl3): δ = 9.29 (br s, 1H, N*H*), 7.55–7.48 (m, 1H, H_{Ar}), 7.45–7.21 (m, 8H, H_{Ar}), 7.14–7.05 (m, 1H, H_{Ar},), 5.08 (d, *J* = 2.9 Hz, 1H, H_{Aliph}), 3.92 (d, J = 2.9 Hz, 1H, H_{Aliph}), 3.85 (s, 3H, C*H*$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.8, 169.6, 148.0, 144.6, 140.9, 137.2, 129.2 (2C), 128.3, 127.6, 127.5 (2C), 123.1, 122.4, 121.4, 113.8, 67.9, 52.9, 44.2 ppm; IR (ATR): *v* = 3266 (br m), 3067 (w), 3028 (w), 2950 (w), 1733 (m), 1676 (s), 1620 (w), 1541 (w), 1486 (w), 1438 (w), 1370 (w), 1320 (m), 1246 (m), 1158 (m), 1101 (w), 1063 (w), 1016 (w), 910 (w), 851 (w), 743 (m), 702 (m), 618 (w), 506 (w), 430 (w) cm^{-1}; HRMS (ESI): m/z calcd. for $C_{19}H_{15}N_1O_3Na_1$ $[M+Na]^+$: 328.0944; found: 328.0944.

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Asymmetric Nazarov Cyclizations Catalyzed by Chiral-at-Metal Complexes

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