Asymmetric Catalysis

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Chiral-at-Metal Octahedral Iridium Catalyst for the Asymmetric Construction of an All-Carbon Quaternary Stereocenter**

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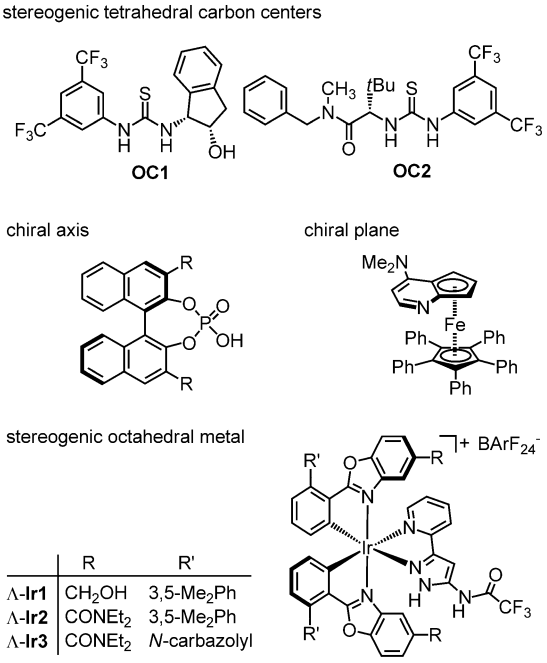
Asymmetric catalysts, whether metal complexes with chiral ligands, chiral organometallics, or chiral organic compounds (organocatalysts), achieve asymmetric induction by transferring chiral information from the catalyst to the substrate(s).[1] The source of the catalyst's chirality therefore plays a crucial role for its mode of action, and is typically derived from one or more tetrahedral stereogenic centers (mostly carbon atoms, but also heteroatoms, such as sulfur or phosphorus), axial chirality, planar chirality, or a combination thereof (Scheme 1). In contrast, only few reports exist of asymmetric catalysts that derive their chirality exclusively from an octahedral stereocenter.[2–4] This seems surprising, considering the prevalence of the octahedral coordination geometry in chemistry and its ability to support the generation of structures with high complexity and, as a result of ligand crowding and chelate effects, often low conformational flexibility.[5] We recently demonstrated the use of chiral-at-metal octahedral complexes for the tailored design of a highly efficient asymmetric noncovalent catalyst that requires low catalyst loading by reporting an inert iridium(III)-based catalyst for the conjugate asymmetric transfer hydrogenation of β,β-disubstituted nitroalkenes.[6] However, excellent metal-, bio-, and organo-catalysts already exist for this transformation,[7] and we were therefore wondering whether an octahedral chiral-at-metal catalyst could be developed for a more challenging asymmetric conversion. In this respect, the asymmetric conjugate addition of carbon nucleophiles to β,β-disubstituted nitroalkenes constitutes a highly attractive reaction as it permits the construction of a stereogenic carbon atom bound to four other carbon substituents (all-carbon quaternary stereocenter).[8] Only a handful of studies are available dealing with this particular reaction, thereby presumably reflecting the involved challenge of overcoming a significant steric repulsion between the incoming carbon nucleophile and the carbon substituents of the nitroalkene electrophile. Nevertheless, Hoveyda and co-workers introduced a Cu-catalyzed dialkylzinc conjugate addition,[9] Arai and co-workers reported a Cu-catalyzed addition of indoles to isatin-derived nitroalkenes,[10] Jia and co-workers disclosed a Ni-catalyzed addition of indoles to β-CF_3-β-disubstituted nitroalkenes,[11] Ricci and co-workers reported a phase-transfer asymmetric organocatalytic conjugate addition of cyanide to β,β-disubstituted nitroalkenes, albeit with only modest enantioselectivities,[12] Melchiorre and co-workers introduced the asymmetric vinylogous Michael addition of cyclic enones to nitroalkenes catalyzed by natural cinchona alkaloids, including one reaction using a β,β-disubstituted nitroalkene,[13] and finally Kastl and Wennemers introduced a proline-peptide-catalyzed asymmetric addition of aldehydes to β,β-disubstituted nitroalkenes under formation of γ-nitroaldehydes.[14] The restricted scope of dialkylzinc reagents and the high catalyst loadings of 10 mol% or more required for the remaining methods confirm the significant difficulty of



	R	R'
Λ-**Ir1**	CH_2OH	3,5-Me_2Ph
Λ-**Ir2**	$CONEt_2$	3,5-Me_2Ph
Λ-**Ir3**	$CONEt_2$	*N*-carbazolyl

Scheme 1. Sources of chirality in asymmetric catalysts. See Ref. [6] (Λ-**Ir1**) and the Supporting Information (Λ-**Ir2** and Λ-**Ir3**) for the synthesis of the enantiopure iridium catalysts. $BArF_{24}^-$ = tetrakis[(3,5-di-trifluoromethyl)phenyl]borate.

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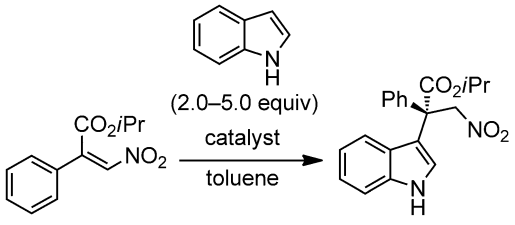
this conversion. Herein, we wish to report the highly efficient catalysis of the conjugate addition of indoles to α-substituted-β-nitroacrylates under the enantioselective construction of an all-carbon quaternary stereocenter using an inert only-chiral-at-metal iridium(III) complex. Although it functions as a nonbonding catalyst, promoting merely three hydrogen bonds, the iridium complex can be employed routinely with catalyst loadings of not more than 1 mol%, while retaining high *ee* values of up to 98%.

We started our study with the previously developed asymmetric transfer hydrogenation catalyst Λ-**Ir1** (Scheme 1).[6] We envisioned that Λ-**Ir1** might be capable of catalyzing the addition of indoles to β,β-disubstituted nitroalkenes by simultaneously activating the nitroalkene electrophile (double hydrogen bond with the amidopyrazole moiety) and the indole nucleophile (single hydrogen bond between the indole-NH and an oxygen lone pair of an OH group), according to a mechanism recently proposed by Ricci and coworkers for the addition of indoles to β-monosubstituted nitroalkenes catalyzed by a bifunctional thiourea.[15] In fact, the reaction of (*Z*)-1-phenyl-2-nitro-isopropylacrylate (**1a**) with indole catalyzed by 5 mol% Λ-**Ir1** at room temperature afforded the expected conjugate-addition product (*S*)-**2a** with a conversion of 71% after three days, but created the all-carbon quaternary stereocenter with a disappointing enantiomeric excess of just 70% (Table 1, entry 1). We speculated that the performance of the catalyst might be improved by replacing the hydroxy group with a stronger hydrogen-bond acceptor and therefore designed the carboxamide-containing catalyst Λ-**Ir2** (Scheme 1), which bears an *N*,*N*-diethylcarboxamide instead of the hydroxymethyl group of Λ-**Ir1**.[16,17] Interestingly, 5 mol% of Λ-**Ir2** catalyzed the reaction **1a**→(*S*)-**2a** with a conversion of 87% after 24 hours and a vastly improved *ee* value of 96% (Table 1, entry 2). Even a reduced catalyst loading of 2 mol% afforded (*S*)-**2a**, still with 93% *ee* in 58 hours (Table 1, entry 3). Replacing the 3,5-dimethylphenyl group by a carbazolyl moiety finally resulted in the further improved catalyst Λ-**Ir3** (Scheme 1). Λ-**Ir3** provides (*S*)-**2a** with a high *ee* of 98% at 2 mol% catalyst loading (Table 1, entry 4). Optimization of the reaction conditions (Table 1, entries 5–7) by increasing the concentration of **1a** (2 M) and indole (5 equiv) further speeded up the reaction so that with 1 mol% of Λ-**Ir3** full conversion is afforded within just 12 h at room temperature (Table 1, entry 7). It is noteworthy that Ricci's thiourea catalyst **OC1**[15] (Scheme 1), at a catalyst loading that is 20 times higher (20 mol%), catalyzes the conversion **1a**→(*S*)-**2a** only with a modest 42% *ee* (Table 1, entry 8). The related carboxamide thiourea catalyst **OC2**[18] (Scheme 1) displayed an even weaker performance with just 10% *ee* at 20 mol% catalyst loading (Table 1, entry 9).

We next investigated the scope of the reaction of nitro substrates with iridium catalyst Λ-**Ir3**. Table 2 shows that the reactions of a variety of 1-aryl-2-nitroacrylates (**1a–i**) with indole in the presence of 1 mol% Λ-**Ir3** provided the products **2a–i** containing the quaternary carbon center in high yields (87–97%) and with excellent enantioselectivities (93–98% *ee*) within 11–15 hours at room temperature (Table 2,

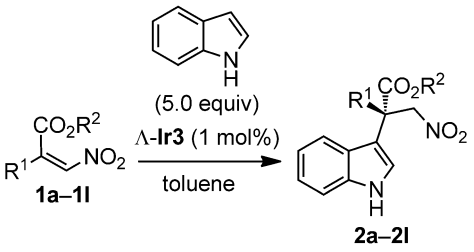
Table 1: Development of a chiral-at-metal iridium(III) complex for the enantioselective Friedel–Crafts alkylation of indole with the β,β-disubstituted nitroalkene **1a**.[a]



Entry	Catalyst	Conditions	*t* [h]	Conv. [%][b]	*ee* [%][c]
1	Λ-**Ir1** (5 mol%)	**1a** (1 M), indole (2 equiv)	72	71	70
2	Λ-**Ir2** (5 mol%)	**1a** (1 M), indole (2 equiv)	24	87	96
3	Λ-**Ir2** (2 mol%)	**1a** (1 M), indole (2 equiv)	58	77	93
4	Λ-**Ir3** (2 mol%)	**1a** (1 M), indole (2 equiv)	36	97	98
5	Λ-**Ir3** (1 mol%)	**1a** (2 M), indole (2 equiv)	24	93	96
6	Λ-**Ir3** (1 mol%)	**1a** (1 M), indole (5 equiv)	24	98	96
7	Λ-**Ir3** (1 mol%)	**1a** (2 M), indole (5 equiv)	<12	100	96
8	**OC1** (20 mol%)	**1a** (2 M), indole (5 equiv)	24	84	42
9	**OC2** (20 mol%)	**1a** (2 M), indole (5 equiv)	24	71	10

[a] Reaction conditions: Nitroalkene **1a** (0.10 mmol), indole (0.20 mmol or 0.50 mmol), and iridium catalyst Λ-**Ir1**-**3** (1–5 mol%) in anhydrous toluene (0.050 mL or 0.10 mL) were stirred at 20°C for the indicated time under argon atmosphere and reduced light. [b] Conversion determined by ^{1}H NMR spectroscopy. [c] Enantiomeric excess determined by HPLC on a chiral stationary phase.

Table 2: Nitroalkene substrate scope of the alkylation of indole with iridium catalyst Λ-**Ir3** generating a quaternary carbon center.[a]

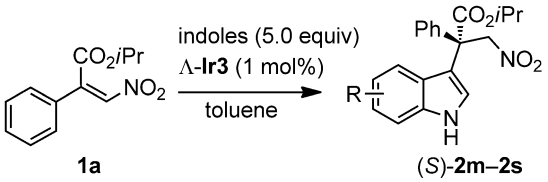


Entry	Substrate (R^1, R^2)	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1a** (Ph, *i*Pr)	(*S*)-**2a**	12	97	96
2	**1b** (Ph, *n*Hex)	(*S*)-**2b**	12	95	96
3	**1c** (Ph, Me)	(*S*)-**2c**	11	92	95
4	**1d** (4-ClC_6H_4, *i*Pr)	(*S*)-**2d**	13	93	95
5	**1e** (4-ClC_6H_4, Et)	(*S*)-**2e**	12	94	95
6	**1f** (4-$MeOC_6H_4$, *i*Pr)	(*S*)-**2f**	15	87	97
7	**1g** (3-$MeOC_6H_4$, Et)	(*S*)-**2g**	12	92	96
8	**1h** (3-ClC_6H_4, Et)	(*S*)-**2h**	12	95	93
9	**1i** (2-thienyl, Et)	(*R*)-**2i**	12	94	98
10	**1j** (*i*Pr, Et)	(*S*)-**2j**	40	82	94
11	**1k** (cyclohexyl, Et)	(*S*)-**2k**	72	72	93
12	**1l** (Me, Et)	(*S*)-**2l**	11 (36)[d]	91 (84)[d]	76 (92)[d]
13[e]	**1a** (Ph, *i*Pr)	(*S*)-**2a**	24	95	93

[a] Reaction conditions: Nitroalkenes **1a–1l** (0.10 mmol), indole (0.50 mmol), and iridium catalyst Λ-**Ir3** (0.0010 mmol) in anhydrous toluene (0.050 mL, 2.0 M) were stirred at 20°C for the indicated time under argon atmosphere and reduced light. [b] Yields of isolated products. [c] Enantiomeric excess determined by HPLC on a chiral stationary phase. [d] Performed at −20°C. [e] Λ-**Ir3** at 0.5 mol%.

entries 1–9). To our delight, Λ-**Ir3** also efficiently converts 1-alkyl-2-nitroacrylates (**1j–l**) to their respective products (*S*)-**2j–l** containing the quaternary carbon center under optimized conditions (Table 2, entries 10–12, 72–84% yield, 92–94% *ee*), although 1-methyl-2-nitroacrylate **1l** requires a reduction of the reaction temperature to −20°C in order to achieve a high *ee* value (Table 2, entry 12). Furthermore, chiral-at-metal iridium catalyst Λ-**Ir3** tolerates electron-acceptor- and electron-donor-substituted indoles **3–8**, as shown in Table 3 (entries 1–7) with the exception of the N-methylated derivative **9**, which provides (*S*)-**2s** only in 79% yield and 76% *ee*. It is worth noting that the catalyst loading can be further reduced while retaining high enantiomeric excess. For example, just 0.5 mol% Λ-**Ir3** catalyzed the conversion **1a**→(*S*)-**2a** within 24 hours in 95% yield with 93% *ee* (Table 2, entry 13).

Table 3: Indole substrate scope of the alkylation of indoles with iridium catalyst Λ-**Ir3** generating a quaternary carbon center.[a]



1a (*S*)-**2m–2s**

Entry	Substrate (R)	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**3** (5-CH_3)	(*S*)-**2m**	12	95	97
2	**4** (5-OCH_3)	(*S*)-**2n**	13	94	93
3[d]	**5** (5-Br)	(*S*)-**2o**	48	78	95
4[d]	**6** (6-OCH_3)	(*S*)-**2p**	17	94	96
5[d]	**7** (6-Cl)	(*S*)-**2q**	25	84	97
6	**8** (7-CH_3)	(*S*)-**2r**	12	96	97
7	**9** (N-CH_3)	(*S*)-**2s**	24	79	76

[a] Reaction conditions: Nitroalkene **1a** (0.10 mmol), indoles (0.50 mmol), and iridium catalyst Λ-**Ir3** (0.0010 mmol) in anhydrous toluene (0.050 mL, 2.0 M) were stirred at 20°C for the indicated time under argon atmosphere and reduced light. [b] Yields of isolated products. [c] Enantiomeric excess determined by HPLC on a chiral stationary phase. [d] Nitroalkenes used at lower concentration (0.10 mL, 1.0 M).

A proposed hydrogen-bonded ternary complex composed of catalyst Λ-**Ir3**, nitroalkene **1a**, and indole (Figure 1a) is based on the mechanistic understanding of bifunctional thiourea catalysis in general,[19,20] the proposed mechanism by Ricci and co-workers for the addition of indoles to β-monosubstituted nitroalkenes in particular,[15] and is consistent with our experimental results of affording the *S* enantiomer of product **2a** with a quaternary carbon center (Figure 1b). Accordingly, the β,β-disubstituted nitroalkene forms two hydrogen bonds with the trifluoroacetamidopyrazole moiety, whereas the NH group of the indole nucleophile forms hydrogen bonds with the carbonyl oxygen atom[15] of the amide moiety. Overall, these three hydrogen bonds lower the activation barrier by rendering the nitroalkene more electrophilic and the indole more nucleophilic, and by bringing electrophile and nucleophile in the proper position for the following C–C bond formation. The enantioselectivity

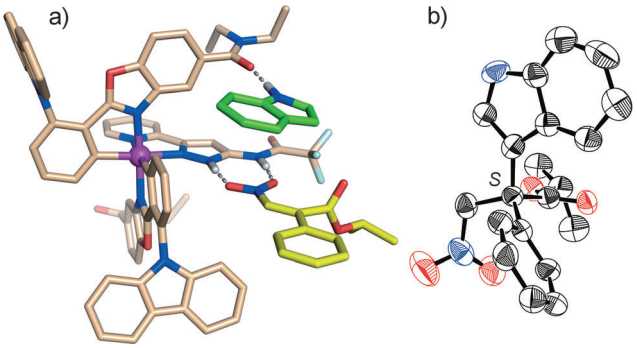


Figure 1. a) Proposed hydrogen-bonded ternary complex composed of catalyst Λ-**Ir3** (beige), nitroalkene **1a** (yellow), and indole (green) leading to the transitions state. The distance between C3 of the indole (carbon nucleophile) and the carbon atom in β position of the nitroalkene (carbon electrophile) is 3.8 Å. The ternary complex was built with the molecular modeling software Scigress (Fujitsu) and represented with The PyMOL Molecular Graphics System, Version 1.3 Schrödinger, LLC. b) ORTEP representation of a crystal structure of (*S*)-**2a** with thermal ellipsoids at 50% probability. Solvent molecules are omitted for clarity.

can be rationalized with a preferred hydrogen-bonding arrangement of the nitroalkene in which the bulky carboxylic ester is pointing away from the carbazole moiety in addition to a preference for the *Si* face in the addition of the indole to the nitroalkene directed by the hydrogen bonding between the amide of the iridium catalyst and the indole NH. The importance of this single hydrogen bond is confirmed by the observed low enantioselectivity upon N methylation of the indole, which prevents a formation of this hydrogen bond (Table 3, entry 7). Furthermore, the amide catalysts Λ-**Ir2** and Λ-**Ir3** are significantly more active and provide the addition product (*S*)-**2a** with higher enantioselectivity compared to Λ-**Ir1** (Table 1), thus demonstrating the superiority of the *N*,*N*-diethylcarboxamide over the hydroxymethyl group as a hydrogen-bond acceptor in this catalysis. This result can be rationalized with a superior hydrogen-bond affinity of the carboxamide over the hydroxy group,[16] in combination with a preferred conformation of the amide group rotated out of conjugation with the benzoxazole moiety because of steric reasons,[21] thereby placing the amide oxygen atom in an ideal position for hydrogen bonding with the indole nucleophile. It is intriguing that the reaction **1a**→(*S*)-**2a** still provides high enantioselectivities (93% *ee*) with just 0.5 mol% Λ-**Ir3** (Table 2, entry 13). With the assumption that under these conditions the undesired enantiomer (*R*)-**2a** is formed predominately from the uncatalyzed background reaction, one can calculate a rate acceleration with catalyst Λ-**Ir3** by a factor of 2.7×10^3.[22] This rate acceleration is even more impressive taking into account that Λ-**Ir3** catalyzes a challenging asymmetric formation of a quaternary carbon center by forming just three hydrogen bonds, and we hypothesize that it is the limited flexibility of the iridium scaffold that keeps the key functional groups in the right orientation, thereby lowering the entropic penalty paid for the highly ordered transition state.

In conclusion, we herein reported an inert iridium-based catalyst that draws its chirality exclusively from an octahedral

stereocenter and highly efficiently catalyzes the challenging construction of a stereogenic all-carbon quaternary stereocenter by merely forming three hydrogen bonds. Beyond demonstrating the scope of hydrogen-bonding catalysis, this work demonstrates the power of inert metal complexes as templates for asymmetric organocatalysis. In this respect, it is our opinion that cyclometalated iridium(III) complexes are especially suitable metal-based scaffolds because of their high substitutional inertness and configurational stability,[23,24] as well as the ability to conveniently access stereoisomers in a nonracemic fashion.[25,26]

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[23] No racemization was observed upon keeping Λ-**Ir3** dissolved in CH_2Cl_2 or MeCN at 20 °C for 7 days (see the Supporting Information). However, as a precaution to prevent any light-induced catalyst racemization, all catalysis reactions were performed under reduced light in brown glass vials.

[24] The catalyst can be recycled several times without any significant loss of catalytic activity, as determined for the conversion **1a** → (*S*)-**2a** with Λ-**Ir3** (1 mol%) starting with a 1 mmol scale: cycle 1 = 96% yield, 97% *ee*; cycle 2 = 95% yield, 97% *ee*; cycle 3 = 98% yield, 96% *ee*. See the Supporting Information for more details.

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