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Restricted Conformation of a Hydrogen Bond Mediated Catalyst Enables the Highly Efficient Enantioselective Construction of an All-Carbon Quaternary Stereocenter

Weici Xu,[1] Xiang Shen,[1] Qiao Ma,[1] Lei Gong,[1*] and Eric Meggers[1,2*]

[1]College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, People's Republic of China

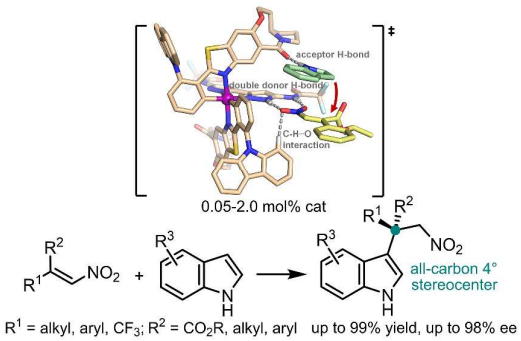
[2]Fachbereich Chemie, Philipps-Universität Marburg, Hans-Meerwein-Strasse 4, 35043 Marburg, Germany

*Corresponding authors: gongl@xmu.edu.cn, meggers@chemie.uni-marburg.de

Abstract: A highly active catalyst for the enantioselective Friedel-Crafts alkylation of indoles with β,β-disubstituted nitroalkenes is reported, allowing catalyst loadings down to 0.05 mol% for this challenging transformation, providing useful synthetic building blocks with an all-carbon quaternary stereocenter. The catalyst is based on a bis-cyclometalated iridium(III) complex as a structural template and through the ligand sphere it forms hydrogen bonds with the two substrates. Starting from a previous design (*Angew. Chem. Int. Ed.* **2013**, *52*, 14021), the catalyst was rendered C_2-symmetrical in order to maximize the atom economy of this catalyst scaffold (two catalytic centers per iridium complex) and, most importantly, rational design was applied to restrict the conformational freedom of a key hydrogen bond acceptor, being responsible for activating the indole nucleophile and bringing it in an ideal position for the presumed ternary transition state.

Keywords: Enantioselective catalysis, iridium, metal template, hydrogen bond formation, Friedel-Crafts alkylation, β,β-disubstituted nitroalkenes, indoles.

TOC-graphic:



Introduction

All-carbon quaternary stereocenters, i.e. carbon atoms that are connected to four different carbon substituents, constitute an important structural element in natural products and pharmaceuticals but their preparation is still a formidable synthetic challenge.[1] In this respect, the catalytic asymmetric Friedel-Crafts alkylation[2,3] of indoles with β,β-disubstituted nitroalkenes has recently gained some attention.[4-9] It provides very versatile building blocks not only containing an all-carbon quaternary stereocenter, but additionally an indole moiety which is an ubiquitous heteroaromatic moiety in natural products and pharmaceuticals,[10] and a nitro group which has been dubbed a "synthetic chameleon"[11] because of its ability to undergo a large variety of useful transformations.[12] In 2013, Jia's group reported the first highly enantioselective Friedel-Crafts alkylation of indoles with β-CF_3-β-disubstituted nitroalkenes for implementing all-carbon quaternary carbon stereocenters using a chiral Ni-BOX catalyst.[4] Later they revealed that β-alkyl-β-disubstituted nitroalkenes and α-aryl-β-nitroacrylates were also tolerated in such catalytic system.[5-7] Arai and co-workers used CuOTf with chiral imidazole-aminophenol ligands to catalyze the asymmetric C3-alkylation of indoles with isatin-derived nitroalkenes to provide optically active 3,3'-bisindoles, which were demonstrated to be potent Wnt signaling inhibitors.[8] Akiyama and co-workers developed an efficient organocatalytic enantioselective Friedel-Crafts reaction of indoles with α-aryl-β-nitroacrylates catalyzed by a chiral phosphoric acid (Figure 1a).[9] Despite these impressive recent advances, issues with respect to reaction scope, reaction conditions, and catalyst loading need to be addressed in order to render this transformation a more practical and attractive strategy for creating all-carbon quaternary stereocenters.[3]

Recently, we introduced iridium-based asymmetric "organocatalysts".[13-15] In this concept, catalysis is mediated exclusively through the organic ligand sphere whereas the substitutionally and configurationally inert iridium center serves as a structural anchor point and furthermore provides the exclusive source of chirality. Such metal-templated catalysts were successfully applied to the enantioselective conjugate reduction of β,β-disubstituted nitroalkenes,[13b,g] asymmetric sulfa-Michael

additions,[13c,d,f] asymmetric aza-Henry reactions,[13c] and the enantioselective Friedel-Crafts alkylation of indoles (Figure 1b).[13a,e] We also demonstrated that our design strategy is suitable for developing an efficient catalyst for the Friedel-Crafts alkylation of nitroacrylates under construction of an all-carbon quaternary stereocenter.[13a] Due to our long-standing interest in evaluating the merit of sophisticated octahedral metal complexes as structural scaffolds for the design of highly efficient asymmetric catalysts for organic transformations, we are striving to improve the performance of such catalysts. Herein, we disclose our successful rational design of a second generation catalyst with significantly improved substrate scope and catalytic activity, allowing catalyst loadings down to 0.05 mol% for the challenging catalytic, enantioselective construction of all-carbon quaternary stereocenters *via* the enantioselective Friedel-Crafts alkylation of indoles with β,β-disubstituted nitroalkenes.

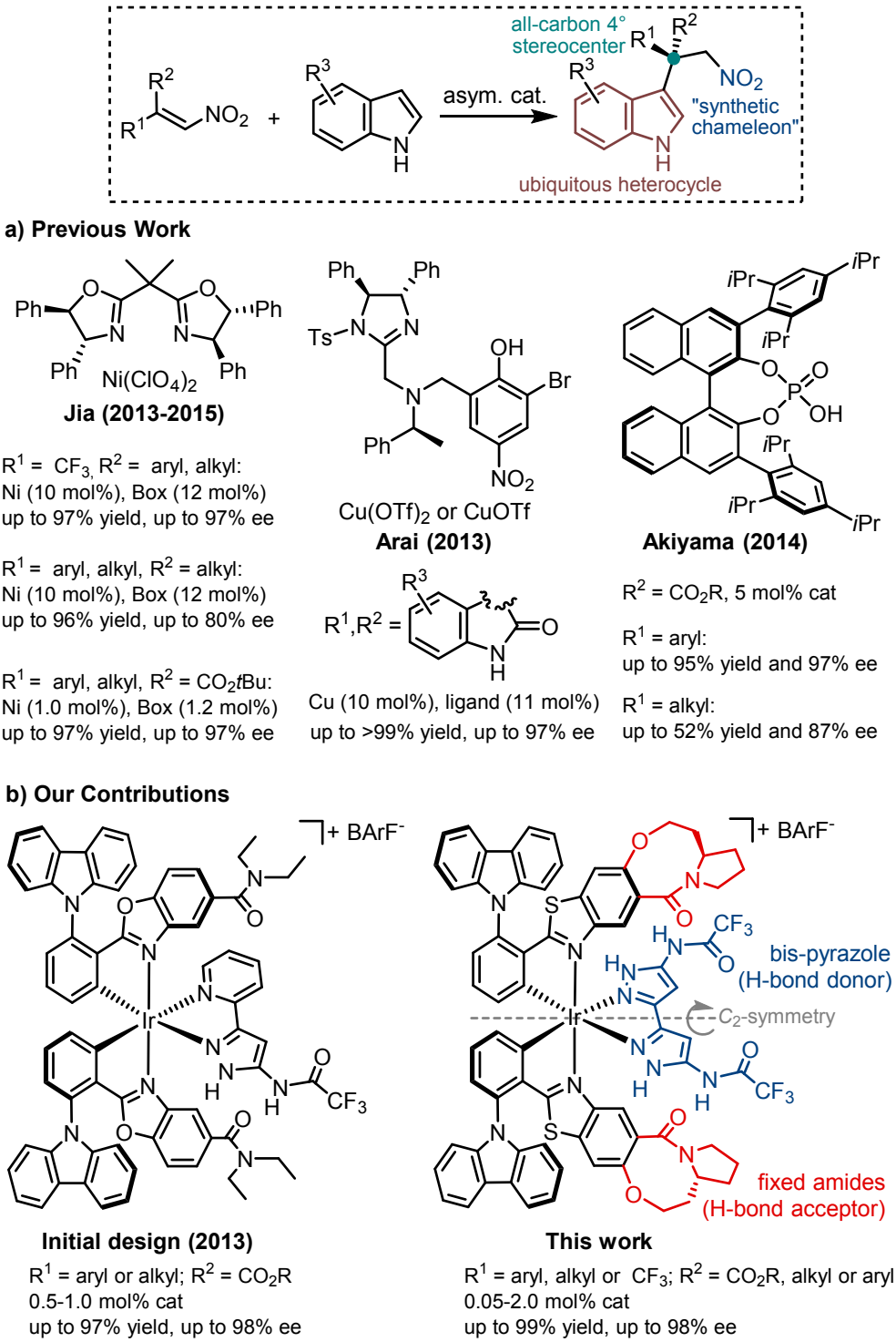
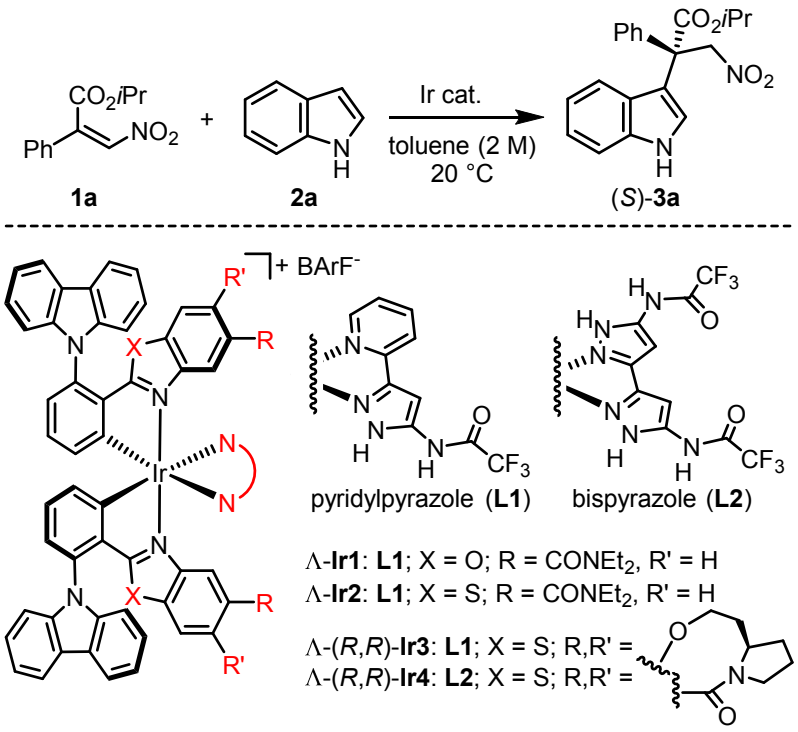


Figure 1. Previous studies and this work regarding the enantioselective Friedel-Crafts alkylation of indoles with β,β-disubstituted nitroalkenes.

Results and Discussion

We previously reported that the iridium complex Λ-**Ir1** catalyzes the reaction of α-aryl-β-nitroacrylate **1a** with indole **2a** to provide the desired Friedel-Crafts alkylation product **3a** containing an all-carbon quaternary stereocenter with 88% conversion and 93% ee within 20 h in toluene at room temperature at a catalyst loading of just 0.5 mol% (Table 1, entry 1).[13a] A modest increase of the reaction rate and enantioselectivity was achieved by empirically replacing the benzoxazole ligands with benzothiazoles (Λ-**Ir2**) (entries 2 and 3). The proposed mechanism proceeds through a ternary complex in which the trifluoroacetamidopyrazole ligand of Λ-**Ir2** forms a double hydrogen bond with the nitroalkene, whereas one *N*,*N*-diethylcarboxamide moiety accepts a hydrogen bond from the indole NH group. Due to steric repulsion, the two ethyl groups force the carboxamide to rotate out of conjugation with the benzothiazole moiety.[16] While multiple conformations are possible, only one leads to a catalytically productive ternary complex, and this conformational flexibility must be entropically unfavorable. Since all three hydrogen bonds are absolutely crucial for the catalytic mechanism, we envisioned that a significantly improvement of the catalytic performance should be achieved by fixing the carboxamide in a conformation that is ideal for catalysis.[17] Modeling the transition state of the reaction and performing conformational analysis suggested that an 8-membered prolinolether-containing lactam should adopt the perfect conformation to assist the catalysis.[18] This was realized with the synthesis of the catalyst Λ-(*R*,*R*)-**Ir3**. Indeed Λ-(*R*,*R*)-**Ir3** at a loading of 0.3 mol% catalyzed the conversion **1a**+**2a**→**3a** with 97% conversion and 97% ee in 14 hours (entry 4). The catalyst loading could be further reduced to 0.1 mol% while still providing a satisfactory conversion of 97% after 36 hours with respectable 93% ee (entry 5). In a final optimization step, we rendered the catalyst C_2-symmetrical by replacing the pyridylpyrazole ligand with a bispyrazole so that the new catalyst Λ-(*R*,*R*)-**Ir4** contains two catalytic sites per iridium complex.[13g] As expected, Λ-(*R*,*R*)-**Ir4** exhibits a further improved catalytic efficiency by providing 90% conversion after 36 hours with 91% ee at a loading of merely 0.05 mol%. With this, a turnover number of 1800 was achieved, which is remarkable for such a challenging asymmetric transformation.[19]

Table 1. Catalyst development.[a]



Entry	Catalyst	Cat. Loading	TON[b]	t (h)	Conv. (%)[c]	ee (%)[d]
1	Λ-**Ir1**	0.5 mol%	176	20	88	93
2	Λ-**Ir2**	0.5 mol%	180	15	90	94
3	Λ-**Ir2**	0.3 mol%	270	22	81	92
4	Λ-(*R,R*)-**Ir3**	0.3 mol%	323	14	97	97
5	Λ-(*R,R*)-**Ir3**	0.1 mol%	970	36	97	93
6	Λ-(*R,R*)-**Ir4**	0.1 mol%	930	22	93	96
7	Λ-(*R,R*)-**Ir4**	0.05 mol%	1800	36	90	91

[a] Reaction conditions: Nitroalkene **1a** (0.10 mmol), indole **2a** (0.50 mmol), and catalyst (0.05-0.5 mol%) in anhydrous toluene (0.050 mL) were stirred at 20 °C for the indicated time. [b] Calculated turnover numbers. [c] Conversion determined by ^{1}H-NMR spectroscopy. [d] Enantiomeric excess determined by HPLC on chiral stationary phase.

In order to verify the conformation of the lactam moiety, we crystallized a model complex Λ-(*R,R*)-**Ir5**, which is derived from Λ-(*R,R*)-**Ir4** by removing the two $COCF_3$ groups and replacing the BArF counterion with chloride. The structure is shown in Figure 2 and confirms that the direction of the carbonyl group is aligned with the N-H hydrogen bond donor groups. Interestingly, the chloride counterion forms a hydrogen bond with the pyrazole N-H group and is below van der Waals distance to one of the C-H groups of the carbazole (3.2 Å).

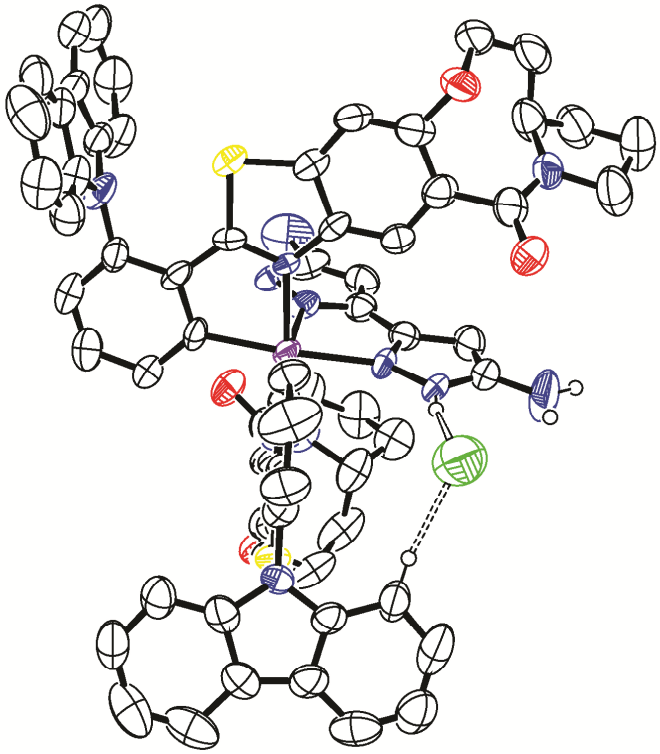


Figure 2. Crystal structure of a model complex (Λ-(*R,R*)-**Ir5**). ORTEP drawing with 50% probability thermal ellipsoids. CCDC number 1483583.

The proposed mechanism proceeds through the ternary complex shown in Figure 3 in which the two NH-groups of the trifluoroacetamidopyrazole moiety form a double hydrogen bond with the nitroalkene. However, nitro groups are very weak hydrogen bond acceptors[20] and we propose that an additional C-H···O interaction, one could call it a weak hydrogen bond, is operative between one oxygen of the nitro group and a C-H group of the carbazole.[21] This is supported by the binding mode

of the chloride in Λ-(*R,R*)-**Ir5** and can also explain why the carbazole is superior to other aromatic moieties at this position.[13a,22] The crystal structure of Λ-(*R,R*)-**Ir5** furthermore demonstrates that the conformation of the 8-membered prolinolether places the carbonyl oxygen of the lactam moiety in a perfect position for accepting a hydrogen bond from the indole. The combination of all three hydrogen bonds electronically activates the substrates and perfectly positions the nitroalkene and indole for a *Si*-face addition of the indole to the β-position of the nitroalkene, and since Λ-(*R,R*)-**Ir4** is C_2-symmetrical, two catalytic reactions can be catalyzed simultaneously. The high rigidity of the catalyst with perfectly positioned catalytically relevant functional groups can be made responsible for the high catalytic activity of Λ-(*R,R*)-**Ir4**.

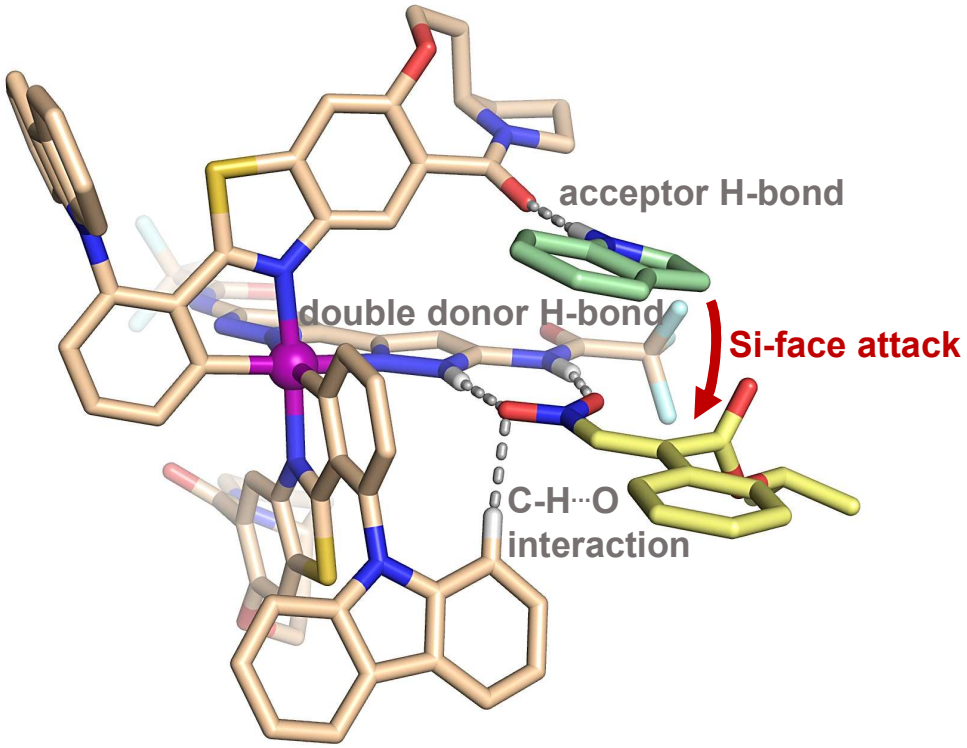
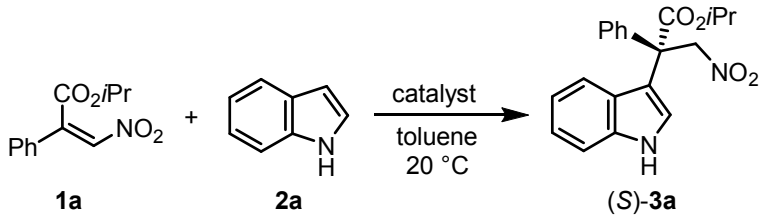


Figure 3. Proposed interaction of the catalyst Λ-(*R,R*)-**Ir4** with nitroalkene **1a** and indole **2a**. The structure of Λ-(*R,R*)-**Ir4** was derived from the crystal structure of the model complex Λ-(*R,R*)-**Ir5.** The ternary complex was built with the molecular modeling softwar Scigress (Fujitsu) and is represented with The PyMOL Molecular Graphics System, Version 1.3 Schrödinger, LLC.

Control experiments support the proposed mechanism and confirm the importance of the position of the lactam carbonyl group (Table 2). Accordingly, the addition of just one equivalent of EtOH or DMF lead to a strong decrease in both of the reaction rate and enantioselectivity, apparently by interfering with the proposed hydrogen-bond-mediated network between the catalyst and substrates (entries 1-3). The presence of one equivalent of nitrobenzene reduces the reaction rate and also slightly affects the enantioselectivity (entry 4), with an additional equivalent of nitrobenzene (entry 5) or using the more electron-rich 4-nitroanisole (entry 6) further affecting yield and enantioselectivity. This can be explained with a competition between nitrobenzene or 4-nitroanisole and the nitroalkene substrate for the triple-hydrogen-bond formation at the catalytic sites. Finally, we probed the importance of the position of the lactam moiety by comparing the catalytic performance of Λ-(*R,R*)-**Ir4** with its diastereomer Δ-(*R,R*)-**Ir4** in which the carbonyl group must point into a different direction. As expected, the diastereomer Δ-(*R,R*)-**Ir4** shows almost no catalytic activity with no significant asymmetric induction (entry 8).

Table 2. Control experiments.[a]



1a **2a** (*S*)-**3a**

Entry	Catalyst	Cat. Loading	Additives	Conv. (%)[b]	ee (%)[c]
1	Λ-(*R,R*)-**Ir4**	0.1 mol%	none	93	96
2	Λ-(*R,R*)-**Ir4**	0.1 mol%	EtOH (1 eq)	44	69
3	Λ-(*R,R*)-**Ir4**	0.1 mol%	DMF (1 eq)	24	20
4	Λ-(*R,R*)-**Ir4**	0.1 mol%	$PhNO_2$ (1 eq)	85	95
5	Λ-(*R,R*)-**Ir4**	0.1 mol%	$PhNO_2$ (2 eq)	80	93
6	Λ-(*R,R*)-**Ir4**	0.1 mol%	*p*-$MeOPhNO_2$ (1 eq)	72	92
7	Δ-(*R,R*)-**Ir4**	0.1 mol%	none	12	3
8	none	-	none	9	n.d.[d]

[a] Reaction conditions: Nitroalkene (0.10 mmol), indole (0.50 mmol), the indicated catalyst, and the indicated additive were stirred in anhydrous toluene (0.050 mL; 0.040 mL for entry 5) at 20 °C for 22 h. [b] Conversion determined by ^{1}H-NMR spectroscopy. [c] Enantiomeric excess determined by HPLC on chiral stationary phase. [d] Not determined.

With the optimized catalyst Λ-(*R*,*R*)-**Ir4** in hand, we next evaluated the substrate scope. As illustrated in Figure 4, in the presence of 0.1 mol% of the catalyst at 20 °C, a range of 1-aryl-2-nitroacrylates containing different ester groups (products **3a**, **b**), electron-donating (products **3c**-**e**) or electron-withdrawing substituents (products **3f**, **g**) within the phenyl moiety, as well as one

heteroaromatic moiety (product **3h**) afford the all-carbon quaternary carbon products **3a**-**h** in high yields (92-99%) and with excellent enantioselectivities (95-98% ee) within 18-28 hours. Moreover, indoles bearing electron-donating (product **3i**) or electron-withdrawing substitutents (product **3j**) (Figure 4), and a methyl substitutent at different positions (products **3k**-**o**) are well tolerated in the reaction, with an exception of using an *N*-methylated indole which provides (*S*)-**3p** only in 25% yield with 47% ee (Figure 5).[23] This is consistent with the proposed mechanism in which a hydrogen bond between the indole N-H and the carboxamide moiety of the catalyst is required for providing an electronic activation and high asymmetric induction. In addition, it is worth noting that the catalytic reaction can be readily scaled up. For example, with 12.2 mg of catalyst Λ-(*R*,*R*)-**Ir4** (0.1 mol%), 1.18 g nitroacrylate **1a** and 2.93 g indole **2a** are converted to 1.75 g (*S*)-**3a** (99% yield) with 96% ee (see more details in the SI).

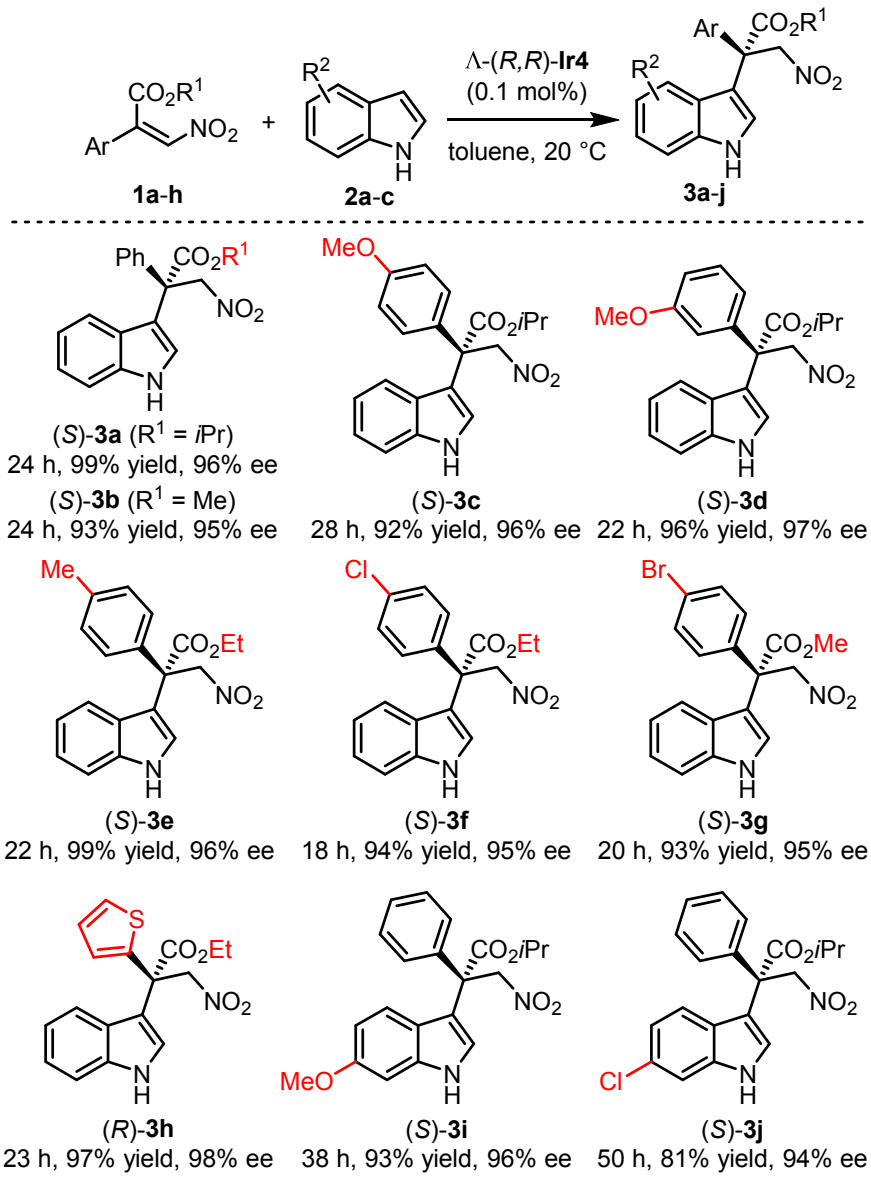


Figure 4. Substrate scope with (*Z*)-1-aryl-2-nitroacrylic esters and indoles using catalyst Λ-(*R,R*)-**Ir4**.

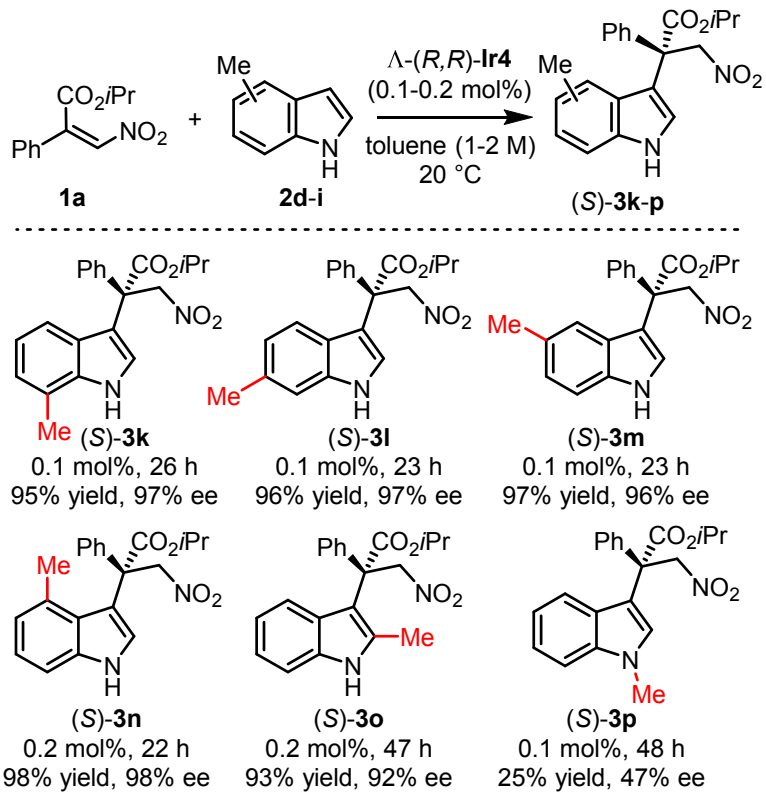


Figure 5. Methyl scan: Friedel-Crafts alkylation of methylindoles with (*Z*)-1-phenyl-2-nitro-isopropylacrylate.

To further investigate generality of the reaction, we next tested other types of β,β-disubstituted nitroalkenes. Figure 6 reveals that α-alkyl-β-nitroacrylates are also suitable substrates as can be seen for the products (*S*)-**3q** (cyclohexyl substituent) and (*S*)-**3r** (methyl substituent) which are formed in high yields (86% and 93%, respectively) and excellent enantioselectivities (98% ee each). In addition, (*E*)-2-phenyl-2-trifluormethyl-nitroethylene, which has been reported to be a useful alkylating reagent for indoles to achieve quaternary stereocenters by Jia *et al.*,[4] is also compatible. With 0.5 mol% of the iridium catalyst, product (*R*)-**3s** is obtained in a 74% yield and with 98% ee in 36 h. Finally, with an increased catalyst loading of 2.0 mol% less reactive β-alkyl-β-aryl nitroalkenes can serve as substrates as can be seen for the formation of (*R*)-**3t** in 61% yield after 48 h with a respectable 81% ee.

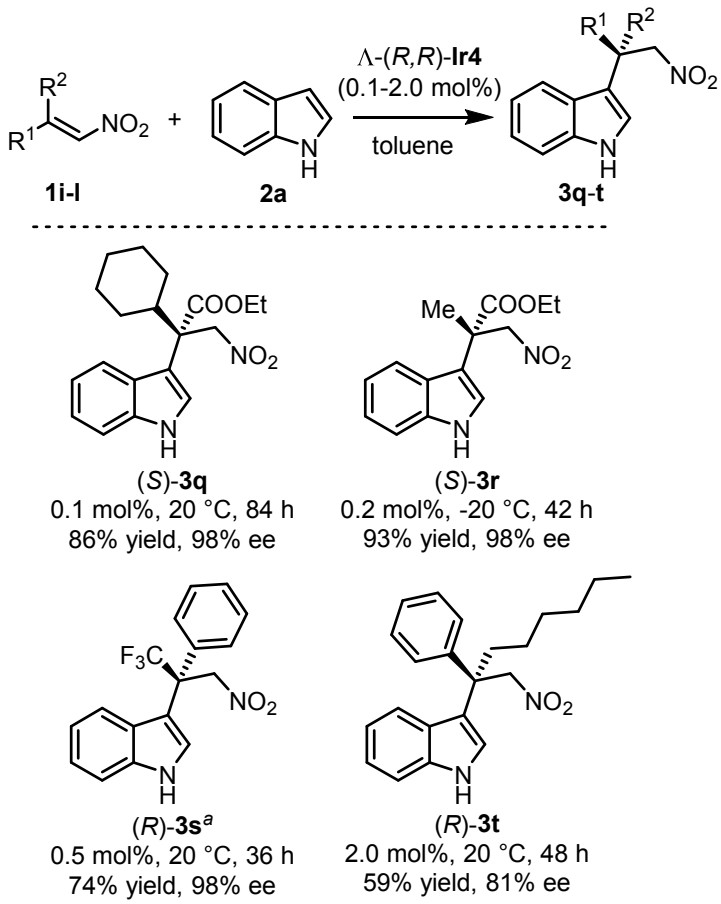


Figure 6. Some additional challenging substrates. [a]Starting from (*E*)-2-trifluoromethyl-1-nitrostyrene.

Conclusions

Herein, we introduced a highly effective asymmetric catalyst for the challenging Friedel-Crafts reaction of indoles with β,β-disubstituted nitroalkenes, providing useful synthetic building blocks which contain an all-carbon quaternary stereocenter. Using a previous catalyst scaffold as a starting point,[13a] we introduced C_2-symmetry in order to maximize the atom economy of this catalysis scaffold thereby obtaining two catalytic centers per iridium complex. Furthermore, we restricted the conformational freedom of a key hydrogen bond acceptor for activating the indole nucleophile and bringing it in a perfect position for the presumed ternary transition state. For this purpose we used an 8-membered prolinolether-containing lactam macrocycle which has the additional advantage that the proline-derived chirality allows for a straightforward synthesis of the catalyst as shown in Figure 7.[24] Efforts to apply this methodology to other nucleophiles[25] and to improve the synthesis of this

structurally sophisticated and highly effective iridium-templated catalyst are ongoing in our laboratory.

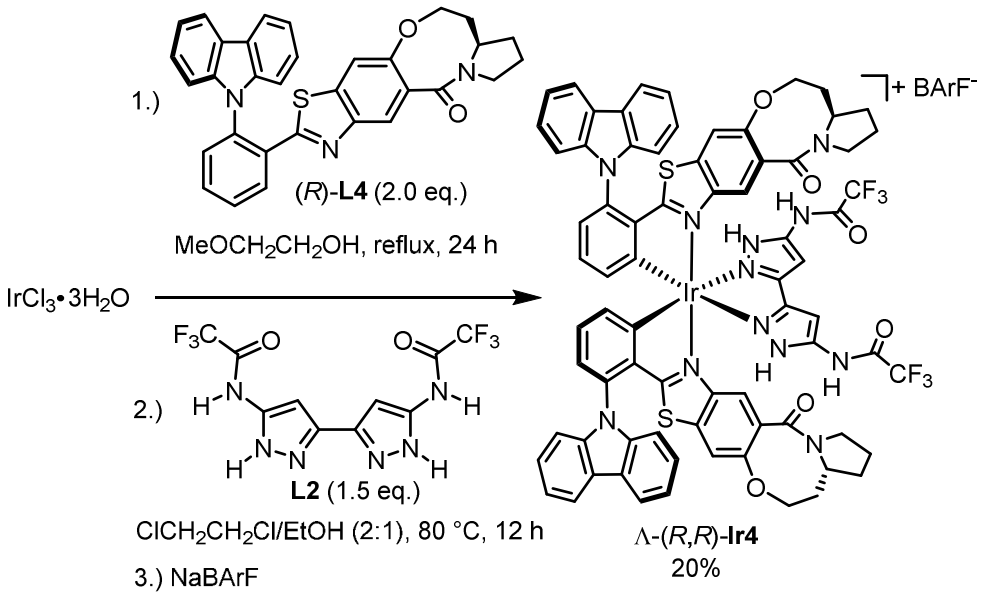


Figure 7. Synthetic route to Λ-(*R,R*)-**Ir4**. See Supporting Information for the synthesis of (*R*)-**L4**.

Supporting Information

Crystallographic data, experimental procedures, analytical data, HPLC traces, and NMR spectra.

Acknowledgements

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(23) 3-Methylindole and 2,3-dimethylindole are not suitable substrates for this transformation. See Supporting Information for more details.

(24) In comparison to our previously developed metal-templated catalysts, Λ-(*R,R*)-**Ir4** can be synthesized without using any auxiliary-mediated resolution strategies. See more details in the Supporting Information.

(25) In an initial experiments, we found that the Friedel-Crafts reaction of 2,5-dimethylpyrrole with alkene **1a** at 40 °C afforded the desired Friedel-Crafts product in 80% yield and with 92% ee using a catalyst loading of merely 0.2 mol% Λ-(*R,R*)-**Ir4**. See Supporting Information for more details.