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Enantioselective 2-Alkylation of 3-Substituted Indoles with Dual Chiral Lewis Acid/Hydrogen-Bond-Mediated Catalyst

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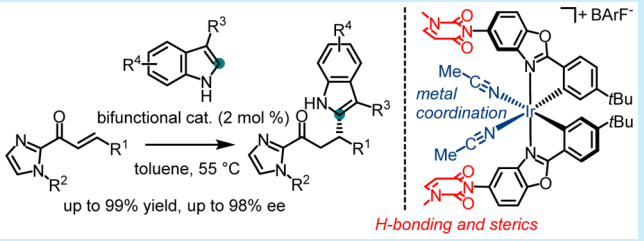
Supporting Information

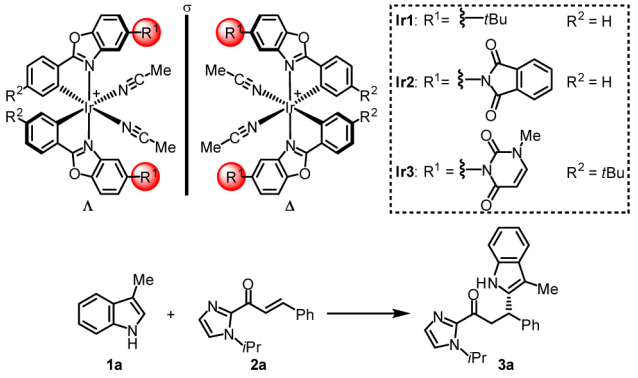
ABSTRACT: A chiral-at-metal bis-cyclometalated iridium complex combines electrophile activation via metal coordination with nucleophile activation through hydrogen bond formation. This new bifunctional chiral Lewis acid/hydrogen-bond-mediated catalyst permits the challenging enantioselective 2-alkylation of 3-substituted indoles with α,β-unsaturated 2-acyl imidazoles in up to 99% yield and with up to 98% enantiomeric excess at a catalyst loading of 2 mol %. As an application, the straightforward synthesis of a chiral pyrrolo[1,2-*a*]indole is demonstrated.



Substituted indoles are a frequent structural element of bioactive compounds. The synthesis of substituted indoles often exploits their high nucleophilicity at the 3-position,[1,2] whereas the electrophilic aromatic substitution of 3-substituted indoles at the 2-position is more challenging and has been much less investigated.[3] For example, only a few studies deal with a direct enantioselective Friedel–Crafts alkylation of indoles at the 2-position.[4−8] In 2013, Chen, Xiao and co-workers reported a highly enantioselective indole C2-alkylation/*N*-hemiacetalization cascade catalyzed by a Cu(II)-bisoxazoline catalyst.[4] Soon thereafter, Feng et al. successfully applied their chiral *N*,*N*′-dioxide–Ni(II) complexes to a Friedel–Crafts C2-alkylation of indoles with β,γ-unsaturated α-ketoesters.[5] Hu and Zhao reported a chiral Brønsted acid catalyzed C2-alkylation of C3-substituted indoles with β,γ-unsaturated α-ketimino esters.[6] Very recently, Jia's group reported an enantioselective Friedel–Crafts C2-alkylation of 3-substituted indoles with α,β-unsaturated esters and nitroalkenes using Cu(II) or Zn(II) bisoxazoline Lewis acid catalysts.[7] Mechanistically distinct, the You group developed very elegant transition-metal catalyzed asymmetric dearomatization reactions to access, among others, five-membered spiroindolenines which can readily undergo an acid-catalyzed stereospecific rearrangement to chiral tetrahydro-1*H*-carbazoles.[8−10] Here, we introduce our progress toward the challenging enantioselective, catalytic Friedel–Crafts C2-alkylation of 3-substituted indoles with α,β-unsaturated 2-acyl imidazoles using a novel dual chiral Lewis acid/hydrogen-bond-mediated catalyst.

Previously, we reported bis-cyclometalated chiral-at-metal[11] iridium(III) and rhodium(III) complexes as versatile chiral Lewis acid catalysts for a variety of transformations,[12] such as the Friedel–Crafts C3-alkylation of indoles with α,β-unsaturated 2-acyl imidazoles.[12a,13] When we tried to apply the catalyst Λ-**Ir1** (PF_6 counterion) to the more challenging Friedel–Crafts C2-alkylation of 3-methylindole **1a** with the α,β-unsaturated 2-acyl imidazole **2a**, the conversion was very sluggish even at the elevated temperature of 55 °C (Table 1, entry 1). Mechanistically, the catalyst functions as a chiral Lewis acid and activates the

Table 1. Catalyst Development[a]



entry	catalyst	counterion	solvent	conv (%)[b]	ee (%)[c]
1	Λ-**Ir1**	PF_6	THF	21	92 (*R*)
2	Λ-**Ir1**	BArF	toluene	24	95 (*R*)
3	Λ-**Ir2**	BArF	toluene	14	88 (*R*)
4	Δ-**Ir3**	BArF	toluene	89	98 (*S*)

[a]Reaction conditions: A solution of α,β-unsaturated acyl imidazole **2a** (0.075 mmol) and the catalyst (0.0015 mmol) in freshly distilled toluene (75 μL) was stirred in a brown glass vial for 20 min at 55 °C. Then 3-methylindole **1a** (0.300 mmol) was added. The reaction mixture was stirred under air at 55 °C for 12 h. [b]Conversion determined by ^{1}H NMR analysis. [c]Ee value determined by HPLC analysis on a chiral stationary phase.

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α,β-unsaturated 2-acyl imidazole by two-point binding, thus improving its electrophilicity. However, this activation by iridium coordination is apparently not sufficient to smoothly promote the desired C2-alkylation of 3-substituted indoles, which display a much reduced HOMO electron density at C2 compared to C3.[8]

Inspired by bifunctional catalysis[14,15] and our previous work on bifunctional metal-templated hydrogen-bond-mediated catalysis for enantioselective Friedel–Crafts alkylations,[16] we wondered if an additional activation of the indole nucleophile through hydrogen bond formation would sufficiently improve the catalytic activity.[17] To achieve this, we synthesized the catalyst Λ-**Ir2**, in which the two *tert*-butyl groups are replaced with two *N*-phthalimides. Furthermore, we replaced the hexafluorophosphate counterion with the hydrophobic tetrakis-[3,5-di(trifluoromethyl)phenyl]borate (BArF) in order to render the catalyst more soluble in hydrogen-bond-promoting unpolar solvents. Unfortunately, no improvement in yields and enantioselectivity were observed (compare entries 2 and 3 of Table 1). We attributed this to the very modest hydrogen bond acceptor cababilities of the imide carbonyl groups and therefore next replaced the *N*-phthalimides with *N*-methyl uracil moieties, since uracil is an established and natural hydrogen bond acceptor.[18] For purely synthetic purposes, we additionally introduced a *tert*-butyl group into the phenyl moieties of the cyclometalating ligands (see Supporting Information). To our delight, Δ-**Ir3** exhibited significantly improved activity by affording the desired product **3a** with 89% conversion after 12 h at 55 °C and with an excellent enantioselectivity of 98% ee (entry 4). The need for an elevated temperature can be attributed to the reduced nucleophilicity of indoles at the 2-position.

The proposed mechanism is shown in Figure 1 and is based on a cocrystal structure of Δ-**Ir3** coordinated to an α,β-unsaturated

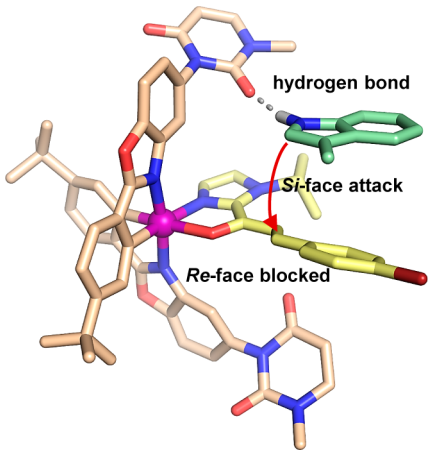
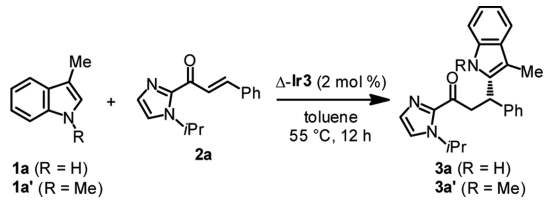


Figure 1. Proposed transition state. 3-Methylindole was positioned into a cocrystal structure of the catalyst Δ-**Ir3** coordinated to an α,β-unsaturated 2-acyl imidazole substrate (CCDC 1496421).

acyl imidazole substrate (bromo-derivatized substrate **2h**) in a bidentate fashion, upon release of the two labile acetonitrile ligands. 3-Methylindole was modeled into the structure forming a hydrogen bond with a carbonyl oxygen atom of one uracil moiety which places the 2-position of the indole in a perfect position for a *Si*-face attack at the electrophilic β-position of the coordinated α,β-unsaturated 2-acyl imidazole substrate. The second uracil moiety is blocking the *Re*-face of the prochiral alkene. This mechanism is consistent with an observed *S*-configured reaction product when using a Δ-configured catalyst.

To probe the proposed hydrogen bond interaction between the catalyst and indole substrate, several control experiments were carried out as shown in Table 2. Accordingly, *N*-methyl

Table 2. Control Experiments To Probe the Hydrogen Bond Interaction during the Catalysis[a]



1a (R = H)
1a' (R = Me)
2a
3a (R = H)
3a' (R = Me)

entry	indole	additive	yield (%)[b]	ee (%)[c]
1[d]	**1a**	none	89	98
2	**1a′**	none	15	91
3	**1a**	ethylene glycol (4 equiv)	51	97
4	**1a**	DMF (4 equiv)	14	93

[a]Reaction conditions: A solution of α,β-unsaturated acyl imidazole **2a** (0.075 mmol) and the iridium catalyst (0.0015 mmol) in the freshly distilled toluene (75 μL) was stirred in a brown glass vial for 20 min at 55 °C. Then **1a** or **1a′** (0.300 mmol) and the indicated additive (0.300 mmol) were added. The reaction mixture was stirred at 55 °C for 12 h under air. [b]Isolated yield. [c]Ee value determined by HPLC analysis on a chiral stationary phase. [d]Taken from entry 4 of Table 1.

protected 3-methylindole (**1a′**), which is unable to donate a hydrogen bond to the uracil moiety of iridium catalyst Δ-**Ir3**, was tested in the reaction with α,β-unsaturated 2-acyl imidazole **2a**. As expected, with 2 mol % of Δ-**Ir3** under our optimized reaction conditions, the 2-alkylated product was only afforded with a yield of 15% within 12 h, compared to 89% using 3-methylindole (entries 1 and 2 of Table 2). However, the reaction still proceeds with satisfactory enantioselectivity (91% ee), thereby revealing that steric effects play an important role for the asymmetric induction (see Figure 1).

The role of the proposed hydrogen bond is also supported by experiments in the presence of competing H-bond donors/acceptors which lead to a decrease in reaction rate and enantioselectivity (Table 2, entries 3 and 4). These experiments strongly support the importance of a hydrogen bond between one of the uracil moieties and the indole substrate which not only increases the reaction rate by rendering the indole substrate more nucleophilic but also provides improved enantioselectivity.

Next, we evaluated the substrate scope with respect to α,β-unsaturated 2-acyl imidazoles. As shown for 12 different α,β-unsaturated 2-acyl imidazoles in Scheme 1, in the presence of 2 mol % of Δ-**Ir3** in toluene at 55 °C, α,β-unsaturated 2-acyl imidazoles containing different substituents at the imidizole nitrogen (products **3b** and **3c**), substituted aromatic moieties (products **3d–j**), a thiophene (product **3k**), or a methyl group (product **3l**) at the β-position are formed in yields of 55–99% yield and 92–98% ee. With respect to 3-substituted indoles, Scheme 2 reveals that 3-methylindoles with an additional methyl group at position 4 to 7 (products **3m–p**) or a methoxy group in position 4 or 5 (products **3q** and **3r**) are well tolerated. The methyl group in the 3-position can also be replaced by a larger aliphatic or aromatic moiety (products **3t** and **3u**). However, electron-withdrawing substituents in the indole moiety fail to provide the desired 2-substituted products as shown for

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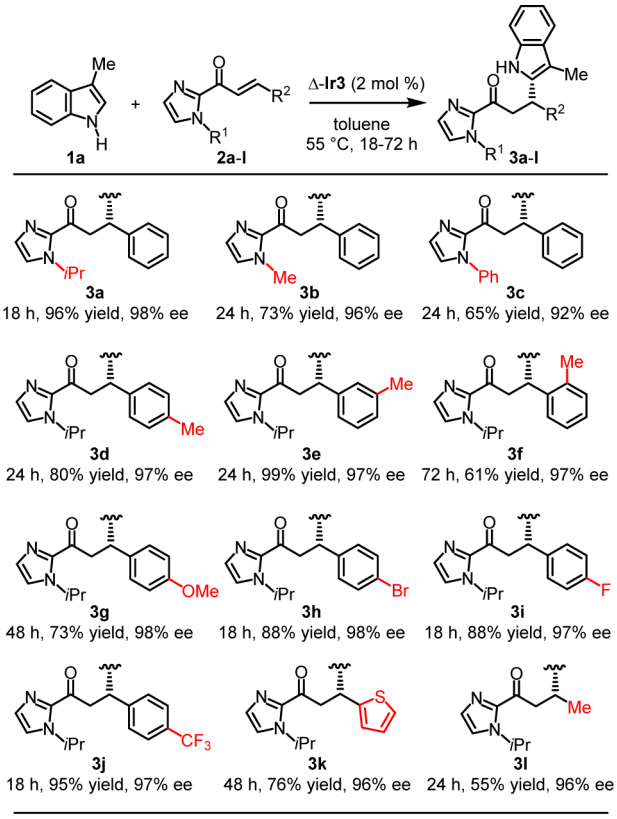
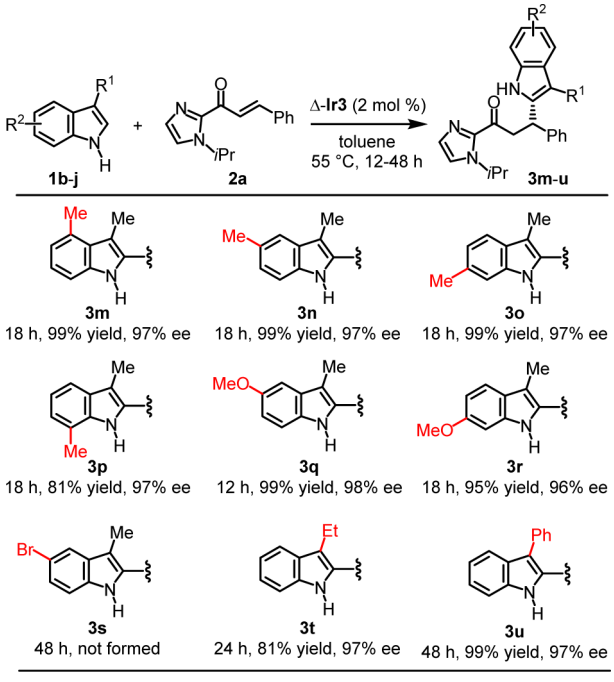
Scheme 1. Scope with Respect to α,β-Unsaturated 2-Acyl Imidazoles



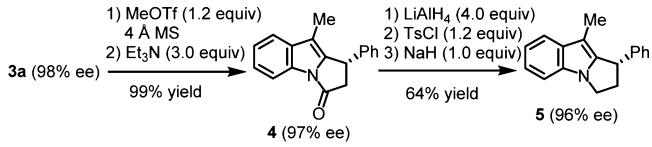
Scheme 2. Scope with Respect to 3-Substituted Indoles



5-bromo-3-methylindole. Instead, an *N*-alkylated side product can be isolated.

The Friedel−Crafts C2-alkylation adducts are valuable chiral building blocks. This is demonstrated for the synthesis of optically active fused tricyclic indoles. Accordingly, treatment of product **3a** (98% ee) with methyl trifluoromethanesulfonate in the presence of 4 Å molecular sieves for 2 h, followed by reacting with triethylamine for 30 min, led to the formation of chiral pyrrolo[1,2-*a*]indol-3(2*H*)-one **4** in almost quantitative yield and with almost complete retention of the stereochemical information (97% ee) (Scheme 3). A subsequent reduction of the

Scheme 3. Follow-up Chemistry with a 2-Alkylated Reaction Product



lactam resulted in the formation of pyrrolo[1,2-*a*]indole **5** in 64% yield and with 96% ee. Such chiral dihydropyrroloindoles are core skeletons for a variety of bioactive compounds, for example the commerically available PKC inhibitor L-888,607.[19]

In conclusion, we developed a bis-cyclometalated iridium catalyst which combines substrate activation by metal coordination and hydrogen bond formation. This new bifunctional chiral Lewis acid/hydrogen-bond-mediated catalyst was applied to the challenging enantioselective 2-alkylation of 3-substituted indoles with α,β-unsaturated 2-acyl imidazoles in up to 99% yield and with up to 98% enantiomeric excess at a catalyst loading of only 2 mol %. X-ray crystallography together with control experiments supports a mechanistic picture in which the α,β-unsaturated 2-acyl imidazole electrophile is activated by bidentate coordination to the iridium, whereas the 3-substituted indole donates a hydrogen bond to one of the uracil moieties, thereby improving the nucleophilicity of the C2-position and increasing the asymmetric induction. Thus, in this system, a single hydrogen bond to the natural hydrogen bond acceptor uracil plays a crucial role in the rate and enantioselectivity of the asymmetric catalysis. Applications to other challenging transformations and the synthesis of the related rhodium catalyst are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03500.

Experimental procedures, full characterization data of all new compounds, X-ray crystallographic data, and chiral HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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