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Iridium-Catalyzed Intramolecular Enantioselective C–H Alkylation at the C-2 Position of *N*-Alkenylindoles

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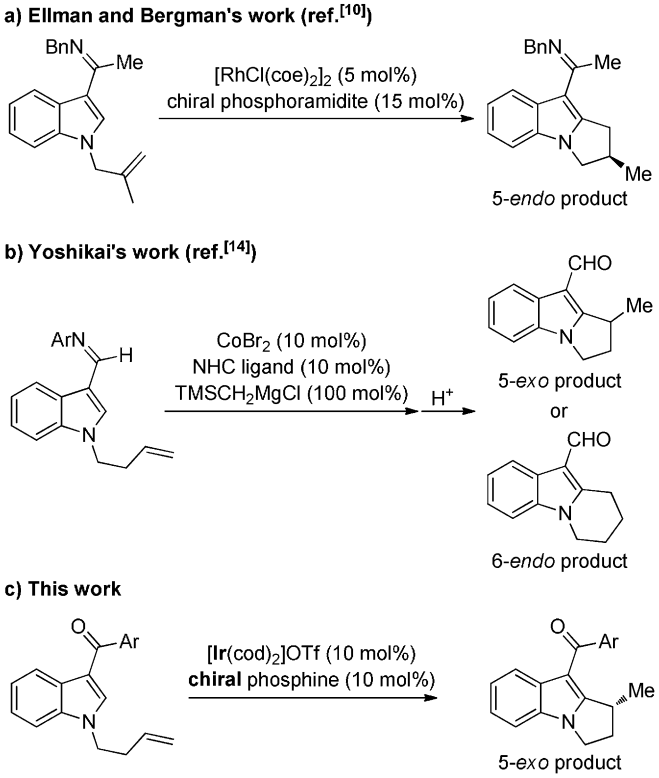
Abstract: Intramolecular enantioselective alkylation of *N*-alkenylindoles proceeded *via* C–H bond cleavage at the C-2 position in the presence of a cationic iridium catalyst with a diphosphine ligand. Aroyl groups at the C-3 position of the indoles operated as effective directing groups, and chiral 1-substituted-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles were obtained in high yield with excellent *ee*.

Keywords: alkylation; C–H activation; enantioselectivity; indoles; iridium catalysts

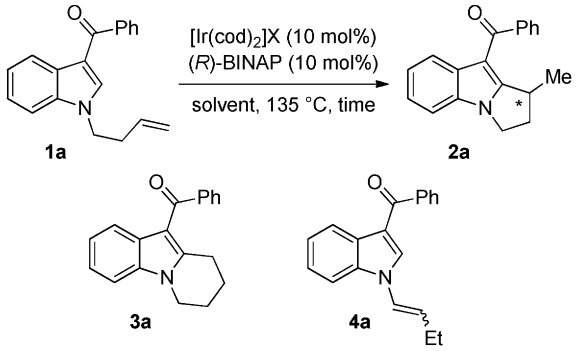
Due to the presence of the indole skeleton in various biologically active compounds, the development of facile methods for regioselective synthesis of substituted indoles is strongly desired.[1] In recent years, direct functionalization initiated by C–H bond cleavage on the indole ring has gradually been superseding the classical protocols, where substituents are installed along with the construction of indole ring, because catalytic C–H bond activation can realize atom- and step-economical protocols.[2] As for the direct C-2 functionalization, C–H arylation and alkenylation have been comprehensively studied,[3] and C–H alkylation has been relatively less developed. Bach reported the first Pd-catalyzed catalytic C–H alkylation by alkyl bromides using a stoichiometric amount of norbornene.[4,5] We have reported the Ir-catalyzed C–H alkylation of *N*-acylindoles by alkenes, where the choice of substituent on the nitrogen atom and diphosphine ligand could control the linear/branch selectivity.[6,7] However, the enantioselective induction in the branched product was moderate (42% *ee*) in the preliminary screening of chiral ligands. Next, Hartwig reported a highly enantioselective C–H alkylation using an Ir-chiral diphosphine ligand catalyst, but the alkene was limited to norbornenes.[8,9]

In contrast, the intramolecular C–H alkylation of *N*-alkenylindoles is fascinating, because it gives *N*-fused tricyclic compounds. Ellman and Bergman reported a pioneering and enantioselective reaction using *N*-allylindoles.[10,11] The imino group at the C-3 position operated as a directing group, and a chiral Rh catalyst gave 5-*endo* type products, which have a stereogenic center at the 2-position of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (Scheme 1a).[12,13] Recently, Yoshikai disclosed a Co-catalyzed reaction of *N*-(but-3-enyl)indoles, where the choice of NHC ligands con-



Scheme 1. Intramolecular C–H alkylations of *N*-alkenylindoles at the C-2 position using directing groups.

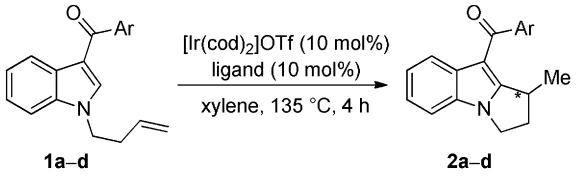
Table 1. Screening of metal complexes and solvents.



Entry	X	Solvent	Time [h]	Yield [%]	*ee* [%]
1	BF_4	PhCl	16	88	58
2[a]	BF_4	PhCl	16	ND[b]	–
3	BARF	PhCl	16	89	70
4	OTf	PhCl	3	89	79
5	OTf	xylene	4	73	91

[a] $[Rh(cod)_2]BF_4$ was used in place of $[Ir(cod)_2]BF_4$.
[b] Not detected.

Table 2. Screening of chiral ligands and directing groups.



Entry	Ar	1	Ligand[a]	Yield [%]	*ee* [%]
1	Ph	**1a**	tolBINAP	59 (**2a**)	95
2	Ph	**1a**	xylylBINAP	57 (**2a**)	91
3	Ph	**1a**	H_8-BINAP	68 (**2a**)	94
4	Ph	**1a**	MeO-BIPHEP	72 (**2a**)	93
5	Ph	**1a**	SEGPHOS	63 (**2a**)	96
6	Ph	**1a**	SYNPHOS	51 (**2a**)	97
7	4-ClC_6H_4	**1b**	SEGPHOS	63 (**2b**)	92
8	4-$MeOC_6H_4$	**1c**	SEGPHOS	90 (**2c**)	92
9	2-naphthyl	**1d**	SEGPHOS	97 (**2d**)	86
10[b]	4-$MeOC_6H_4$	**1c**	SEGPHOS	86 (**2c**)	98
11[c]	4-$MeOC_6H_4$	**1c**	SEGPHOS	66 (**2c**)	96

[a] The *S*-isomer of each ligand was used. tolBINAP = 2,2′-bis([di(*para*-tolyl)phosphine]-1,1′-binaphthyl, xylylBINAP = 2,2′-bis[di(3,5-xylyl)phosphine]-1,1′-binaphthyl, H_8-BINAP = 2,2′-bis(diphenylphosphino)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl, MeO-BIPHEP = 5,5′-dimethoxy-2,2′-bis(diphenylphosphino)biphenyl, SEGPHOS = 5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole, SYNPHOS = 6,6′-bis(diphenylphosphino)-2,2′,3,3′-tetrahydro-5,5′-bi-1,4-benzodioxin.
[b] The reaction was examined at 120 °C.
[c] The reaction was examined at 100 °C.

trolled the selective formation of 5-*exo* and 6-*endo* product, respectively (Scheme 1b).[14] We here report an Ir-catalyzed reaction of *N*-(but-3-enyl)indoles using aroyl groups as directing groups (Scheme 1c).[15] The 5-*exo* type cyclization created a stereogenic center at the 1-position of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole.[16,17]

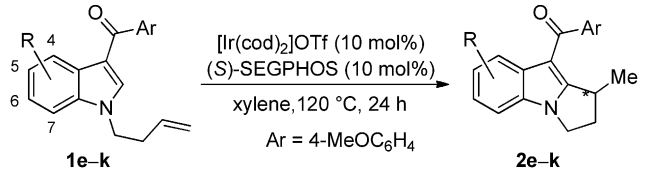
We chose the benzoyl group as a model directing group and subjected *N*-(but-3-enyl)indole **1a** to the intramolecular C–H alkylation (Table 1). When cationic iridium with BINAP was used as a chiral catalyst,[18] the 5-*exo*-cyclized product **2a** was obtained as sole product in high yield with moderate *ee* and the 6-*endo*-cyclized product **3a** was not obtained (entry 1). The Rh counterpart gave enamine **4a** ($E/Z = 4/1$) as an isomerized product and the cyclized product **2a** could not be detected at all (entry 2). The effect of the counter anion of iridium on the enantioselectivity was significant: when triflate was used, the reaction was concluded within 3 h and the *ee* was improved to *ca.* 80% (entry 4). The choice of solvent was also important: the enantioselectivity increased to *ca.* 90%, when the reaction was run in xylene (entry 5).

We next screened the chiral ligands (Table 2, entries 1–6). Among BINAP derivatives (entries 1–3), tolBINAP realized the best *ee* of 95%. Biaryl ligands possessing oxygen functionalities were also effective in this reaction. Excellent *ee*s were achieved by SEGPHOS and SYNPHOS, and we chose SEGPHOS for further investigation (entries 4–6).[19] In each entry, however, a significant amount of isomerized product **4a** was obtained as a by-product. We further examined the effect of the directing group (entries 7–9). When *para*-anisoyl and 2-naphthoyl groups were installed at the C-3 position, the formation of the enamine was suppressed and the yield drastically increased at the cost of a slight decrease in *ee* (entries 8 and 9). By lowering the reaction temperature to 120 °C, both high yield and excellent *ee* were achieved (entries 10 and 11). We selected entry 10 as the optimal reaction conditions.

Table 3 shows the scope of substituents on *N*-(but-3-enyl)indole. An electron-donating methoxy group could be installed at the 4- or 5-position, and the corresponding chiral tricyclic compounds **2e** and **2f** were obtained with high *ee*s (entries 1 and 2). A bromo group gave contrasting results: the reaction of 4-bromoindole **1g** did not proceed at all,[20] while 5-bromoindole **1h** reacted with high enantioselectivity (entries 3 and 4). The bromo-substituted product **2h** furnished a single crystal and its absolute configuration was determined to be the *R*-isomer by X-ray analysis.[21] Indoles **1i** and **1j** possessing a fluoro group at 6- and 7-positions, respectively, were prefered substrates (entries 5 and 6). This reaction was sensitive to steric effects: 7-methylindole **1k** gave cyclized product **2k**, albeit with poor *ee* (entry 7).

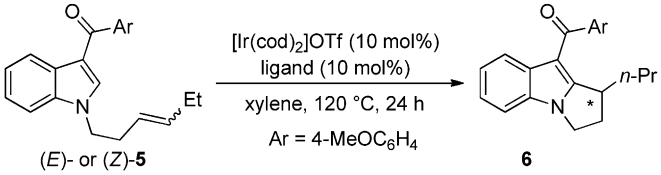
We next examined the reaction of aroylindole **5**, which has an internal olefin tether on its nitrogen atom (Table 4). The stereochemistry of the olefin

Table 3. Scope of substituents on *N*-(but-3-enyl)indole.



Entry	R	**1**	Yield [%]	*ee* [%]
1	4-OMe	**1e**	81 (**2e**)	91
2	5-OMe	**1f**	70 (**2f**)	85
3	4-Br	**1g**	NR	–
4	5-Br	**1h**	61 (**2h**)	91
5	6-F	**1i**	77 (**2i**)	97
6	7-F	**1j**	81 (**2j**)	88
7	7-Me	**1k**	68 (**2k**)	37

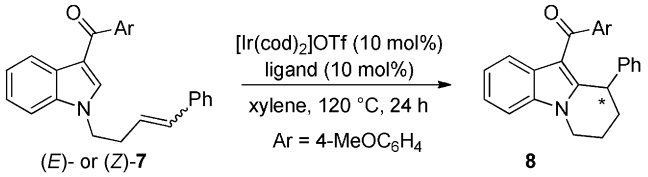
Table 4. Reaction of indole **5** with an internal olefin tether.



Entry	**5**	Ligand[a]	Yield [%]	*ee* [%]
1	(*E*)-**5**	SEGPHOS	75	49
2	(*Z*)-**5**	SEGPHOS	81	90
3	(*Z*)-**5**	DM-SEGPHOS	73	93
4	(*Z*)-**5**	xylylBINAP	74	98

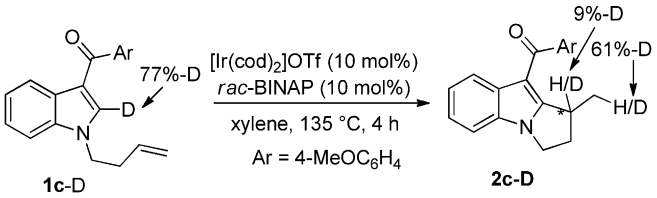
[a] The *S*-isomer of each ligand was used. DM-SEGPHOS = 5,5′-bis[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole.

Table 5. Reaction of indole **7** with an internal olefin tether.

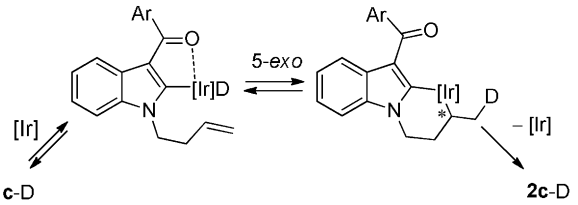


Entry	**7**	Ligand[a]	Yield [%]	*ee* [%]
1	(*E*)-**7**	SEGPHOS	94	33
2	(*Z*)-**7**	SEGPHOS	87	74
3	(*Z*)-**7**	xylylBINAP	98	84

[a] The *S*-isomer of each ligand was used.



Scheme 2. Reaction of **1c**-D.



Scheme 3. Possible mechanism by 5-*exo*-type cyclization.

moiety led to a major difference in the enantioselectivity, and the *Z* isomer gave a much better *ee* (entries 1 and 2). As a result of further ligand screening, xylylBINAP gave rise to an excellent enantioselectivity (entry 4).

In the reaction of aroylindole **7**, which has a benzylidene moiety at the end of a tether on its nitrogen atom, 6-*endo*-type cyclization predominantly proceeded to construct a chiral six-membered system (Table 5). The reaction of the *Z* isomer using xylylBINAP achieved a high enantioselectivity as with aroylindole **5** (entry 3).

As a preliminary mechanistic study, we examined the reaction of **1c**-D using the Ir-*rac*-BINAP catalyst (Scheme 2).[22] Most of deuterium was transferred to the methyl group as expected, but a slight deuteration was observed at the methine moiety on the pyrrolidine ring. Scheme 3 shows a possible mechanism: the C–H bond at the C-2 position was cleaved, intramolecular hydroiridation created a stereogenic center, and subsequent reductive elimination gave the chiral 5-*exo*-type product.[23] The minor deuteration at the methine moiety can be explained *via* reversible *endo*-type alkene insertion *via* a 7-membered iridacycle.[14]

In conclusion, we have developed an intramolecular and enantioselective C-2 alkylation of *N*-alkenylindoles. A *para*-anisoyl group at the C-3 position of the indoles operated as an efficient directing group, and the combination of cationic Ir(I) and chiral diphosphine ligands achieved excellent enantioselectivity. Studies to elucidate the detailed reaction mechanism and on synthetic applications of the chiral indole-containing tricyclic compounds are underway in our laboratory.

Experimental Section

Typical Experimental Procedure of Table 3

$[Ir(cod)_2]OTf$ (0.01 mmol), (*S*)-SEGPHOS (0.01 mmol), and substituted *N*-(but-3-enyl)indole (**1**, 0.10 mmol), were placed in a Schlenk tube, which was then evacuated and backfilled with argon (×3). To the reaction vessel was added anhy-

drous xylene (0.5 mL, pretreated by argon bubbling for 30 sec). The solution was then stirred at 120 °C (bath temperature) for 24 h. The reaction mixture was cooled to room temperature and the solvent was evaporated to dryness. The obtained crude products were purified by thin-layer chromatography to give analytically pure tricyclic product **2**.

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[19] The reaction of 3-acetyl-*N*-(but-3-enyl)indole also smoothly proceeded under the same reaction conditions, but the enantioselectivity was significantly decreased (80%, 75% *ee*).

[20] The cycloadduct could not be detected even at a higher reaction temperature (135 °C).

[21] The stereo structure as analyzed by X ray diffraction is shown in the Supporting Information. CCDC 1038938 contains the supplementary crystallographic data 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.

[22] The deuterium content was decreased by the introduction of a butenyl group to 3-(*para*-anisoyl)indole under the basic conditions.
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