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Ir(I)-Catalyzed C−H Bond Alkylation of C2-Position of Indole with Alkenes: Selective Synthesis of Linear or Branched 2-Alkylindoles

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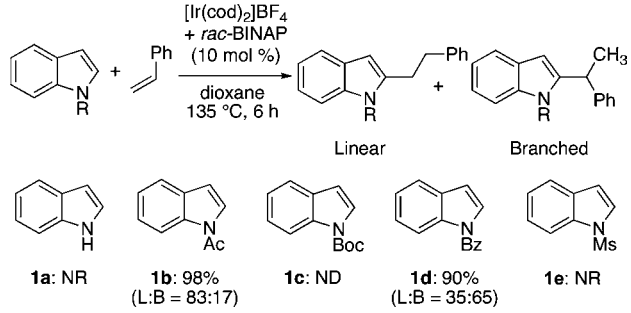
Supporting Information

ABSTRACT: A cationic iridium-catalyzed C2-alkylation of *N*-substituted indole derivatives with various alkenes has been developed, which selectively gives linear or branched 2-alkylindoles in high to excellent selectivity. This protocol relies on the use of the carbonyl group on the nitrogen atom of indole as a directing group: a linear product was predominant when an acetyl group was used as a directing group, and a branched product was predominant with a benzoyl group.

Indole is an important structural unit and is widely found in heterocyclic compounds with biological and medicinal applications.[1] Thus, the efficient functionalization of indole derivatives has attracted much attention from both academia and industry, especially with regard to C−H bond activation based on transition-metal catalyses.[2] In extensive studies using various metal catalysts over the past decade, regioselective C−H bond arylation and alkenylation of indole at the C2- and C3-positions has been reported.[3] Regarding the alkylation of indole derivatives, the C3-alkylation of indole can be achieved by catalytic methods, such as Friedel−Crafts alkylation, allylic alkylation, and conjugated addition.[4] However, there have been relatively few studies on the C2-alkylation of indole.[5] Although C2-alkylation of indole can be achieved through C2-lithiation of *N*-protected indoles,[6] efficient methods for direct C2-alkylation of indole are rare. Notably, 2-alkylindoles serve as precursors for a variety of medicinally important alkaloids and their analogs; for example, 2-(arylethyl)indoles have been used to create indoleamine 2,3-dioxygenase (IDO) inhibitors.[7] Examples of direct C2-alkylation via transition-metal catalyzed C−H activation are still limited, and only a Pd-catalyzed example has been recently reported, which underwent a norbornene-mediated migration of the palladium species from the C3- to C2-position via C−H bond activation of indole.[8] Therefore, the direct C2-alkylation of indole is in high demand. We report here a regioselective C−H bond alkylation of indole with alkenes at the C2-position using a cationic Ir catalyst, which gave linear and branched 2-alkylindoles, respectively, in high to excellent selectivity depending on the choice of the directing group and the ligand of the Ir catalyst.

We have developed cationic iridium-catalyzed reactions initiated by C−H bond activation.[9] Based on the reported protocols, we studied a cationic Ir-catalyzed direct C2-alkylation of indole via C−H bond activation. Our preliminary studies in this area focused on the identification of an appropriate directing group. To this end, free N−H indole and a range of *N*-substituted indoles were subjected to the reaction with styrene in dioxane in the presence of 10 mol % Ir-*rac*-BINAP complex at 135 °C (bath temperature) (Scheme 1).

Scheme 1. Relative Reactivity of *N*-Substituted Indoles



We were delighted to obtain 2-alkylindoles using acetyl and benzoyl groups as directing groups, which can be removed under a variety of reaction conditions.[10] Interestingly, in the reaction of *N*-acetylindole (**1b**) with styrene, linear 2-alkylindole was a major product, while, in the reaction of *N*-benzoylindole (**1d**), branched 2-alkylindole was a major product.[11]

With two effective directing groups in hand, we next focused on improving linear/branched selectivity and examined several diphosphine ligands (Table 1). Initially, an acetyl group was used as a directing group for the selective formation of linear 2-alkylindole (entries 1−6). Among the BINAP derivatives, tolBINAP (**L1**) and xylylBINAP (**L2**) realized good yields with good selectivity; in particular, the ratio reached 90:10 when **L2** was used as a ligand (entries 1 and 2). A more bulky BINAP ligand (**L3**) showed lower reactivity and worse selectivity (entry 3). When a high combined yield was achieved with SEGPHOS (**L4**), the ratio was not improved (entry 4). When DM-SEGPHOS (**L5**) was used, the desired products were obtained in 81% yield in total with a promising ratio (entry 5). With further optimization, DM-SEGPHOS (**L5**) gave the products in 92% yield in total and the ratio was improved to 95:5 when 1,2-dimethoxyethane (DME) was used as a solvent at 75 °C, but a longer reaction time was required (entry 6). We further used a benzoyl group as a directing group for the selective formation of branched 2-alkylindole (entries 7−11). While screening

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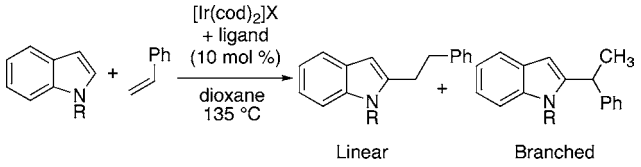
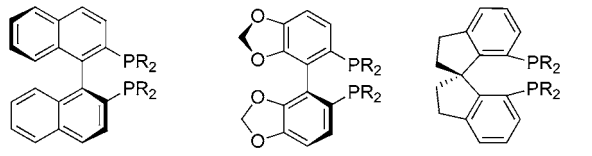
Table 1. Optimization of Reaction Conditions[a]





L1: R = 4-MeC$_6$H$_4$
L2: R = 3,5-Me$_2$C$_6$H$_3$
L3: R = 4-OCH$_3$-3,5-*t*-Bu$_2$C$_6$H$_2$
L4: R = Ph
L5: R = 3,5-Me$_2$C$_6$H$_3$
L7: R = Ph
L8: R = 4-MeC$_6$H$_4$
L9: R = 3,5-Me$_2$C$_6$H$_3$

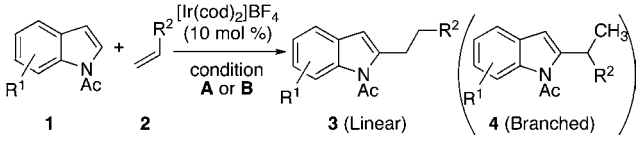
entry	R	X	ligand	*t* (h)	yield (%)	L:B[b]
1	Ac	BF_4	**L1**	6	98	85:15
2	Ac	BF_4	**L2**	6	79	90:10
3	Ac	BF_4	**L3**	6	24	64:34
4	Ac	BF_4	**L4**	6	92	88:12
5	Ac	BF_4	**L5**	6	81	90:10
6[c]	Ac	BF_4	**L5**	48	92	95:5
7	Bz	BF_4	**L6**[d]	6	98	17:83
8	Bz	BF_4	**L7**	24	16	4:96
9	Bz	BARF[e]	**L7**	48	92	2:98
10	Bz	BARF[e]	**L8**	48	87	4:96
11	Bz	BARF[e]	**L9**	48	86	8:92

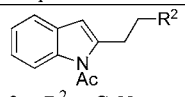
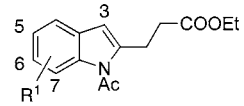
[a]Conditions: indole (0.1 mmol), styrene (0.4 mmol), catalyst (0.01 mmol), ligand (0.01 mmol), dioxane (0.2 mL), at 135 °C (bath temperature), unless otherwise noted. [b]The ratio of linear to branched products was determined by ^{1}H NMR. [c]1,2-Dimethoxylethane (DME) was used as solvent, and the bath temperature was 75 °C. [d]1,1′-Bis(diphenylphosphino)ferrocene (DPPF). [e]BARF: tetrakis(3,5-bis(trifluoromethyl)phenyl)borate.

BINAP derivatives did not improve the branched/linear ratio, DPPF (**L6**) gave the desired products in excellent yield in total with good branched selectivity (entry 7). To our delight, SDP (**L7**) gave the products in excellent selectivity, albeit in low yield. As a result of counteranion screening, BARF dramatically improved the yields, and the branched/linear ratio reached 98:2 (entries 8 and 9). SDP derivatives (**L8**, **L9**) were also tested, but the selectivity did not exceed those with SDP (**L7**) (entries 10 and 11). Therefore, the reaction of *N*-acetylindole was examined under the conditions of entry 6 for the selective synthesis of linear 2-alkylindole, and that of *N*-benzoylindole was examined under the conditions of entry 9 for the selective synthesis of branched 2-alkylindole.

Subsequently, the scope of *N*-acetylindoles and styrene derivatives was examined using an Ir-DM-SEGPHOS catalyst (condition **A**) (Table 2). A wide range of substituents could be used in the reaction, and moderate to good yields and high selectivity were achieved (entries 1−9). In the reaction of styrene derivatives with an electron-donating group, the selectivity of linear to branched products was slightly decreased, but still high (entries 1−6). The steric effect played an important role in this reaction, and *ortho*-bromo-substituted styrene gave the product **3i** in low yield (entry 9). In the reaction with acrylonitrile (condition **B**), the Ir-*rac*-BANAP catalyst realized perfect linear selectivity along with acceptable yields (entry 10). Methyl vinyl ketone was also a suitable substrate for this reaction and afforded the corresponding linear product **3k** with perfect selectivity, albeit in low yield (entry 11). The reaction of ethyl acrylate proceeded smoothly to give

Table 2. Reaction of *N*-Acetylindoles 1 with Alkenes 2[a]



entry	products	cond.[b]	*t* (h)	yield (%)	3:4[c]
					
1	**3a**, R^2 = C_6H_5	**A**	48	92	95:5
2	**3b**, R^2 = 4-$MeOC_6H_4$	**A**	48	75	91:9
3	**3c**, R^2 = 4-MeC_6H_4	**A**	48	67	93:7
4	**3d**, R^2 = 4-FC_6H_4	**A**	21	77	95:5
5	**3e**, R^2 = 4-ClC_6H_4	**A**	48	75	97:3
6	**3f**, R^2 = 4-BrC_6H_4	**A**	48	68	96:4
7	**3g**, R^2 = 3-FC_6H_4	**A**	48	89	97:3
8	**3h**, R^2 = 3-BrC_6H_4	**A**	48	80	98:2
9	**3i**, R^2 = 2-BrC_6H_4	**A**	48	15	95:5
10	**3j**, R^2 = CN	**B**	72	47	>99:<1
11	**3k**, R^2 = $COCH_3$	**B**	24	27	>99:<1
					
12	**3l**, R^1 = H	**B**	6	98	>99:<1
13	**3m**, R^1 = 3-Me	**B**	6	98	>99:<1
14	**3n**, R^1 = 5-Br	**B**	9	70	>99:<1
15	**3o**, R^1 = 6-F	**B**	6	92	>99:<1
16	**3p**, R^1 = 7-Me	**B**	6	92	>99:<1

[a]Conditions: acetylindole **1** (0.1 mmol), alkene **2** (0.4 mmol), $[Ir(cod)_2]BF_4$ (0.01 mmol), unless otherwise noted. [b]Conditions: **A**: (*S*)-DM-SEGPHOS (**L5**, 0.01 mmol), DME (0.2 mL), 75 °C (bath temperature); **B**: *rac*-BINAP (0.01 mmol), dioxane (0.2 mL), 135 °C (bath temperature). [c]The ratio of linear to branched products was determined by ^{1}H NMR.

the alkylated product **3l** in excellent yield with perfect linear selectivity (entry 12). The scope of substituted *N*-acetylindole was investigated by the reaction with ethyl acrylate (entries 13−16). Notably, perfect linear selectivity was achieved in all cases.

We next investigated the scope of *N*-benzoylindole and alkenes (Table 3). A wide variety of substituted styrenes were used for generation of the corresponding branched 2-alkylindoles with excellent selectivity (entries 1−5).[12] Styrene that contained a strongly electron-donating group, such as a methoxy group, gave the desired product in low yield, but the selectivity was excellent. When DPPF was used as a ligand, the same reaction gave the product **6b** in good yield in 24 h, and the ratio of branched to linear product reached 96:4 (entries 2 and 3).[13] 4-Methyl- and 4-chloro-substituted styrenes led to the corresponding products in respective yields of 86% and 50% in total, and the branched/linear ratio was excellent (entries 4 and 5). The results indicated that the electron effect plays an important role in this reaction. The scope of substituted *N*-benzoylindole was investigated in the presence of styrene (entries 6−9). 3-Methyl-*N*-benzoylindole gave **6e** and **7e** in a high combined yield; however, the selectivity of branched and linear products was poor, probably due to a steric effect (entry 6). 6-Fluoro-*N*-benzoylindole gave branched product **6f** in high yield with excellent selectivity (entry 7). The reaction of 7-methyl-*N*-benzoylindole gave branched product **6g** in excellent selectivity, and DPPF gave the better yield (entries 8 and 9).

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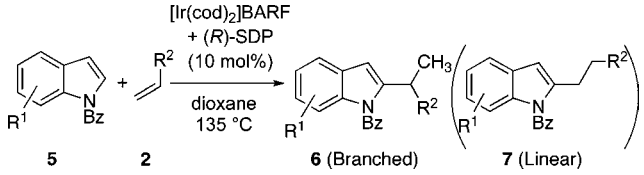
Table 3. Reaction of *N*-Benzoylindoles 5 with Alkenes 2[a]

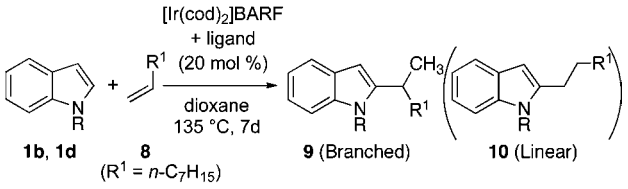


entry	products	*t* (h)	yield (%)	**6**:**7**[b]
1	**6a**, $R^2 = C_6H_5$	48	93	98:2
2	**6b**, $R^2 = 4\text{-}MeOC_6H_4$	96	20	>99:<1
3[c]	**6b**, $R^2 = 4\text{-}MeOC_6H_4$	24	75	96:4
4	**6c**, $R^2 = 4\text{-}MeC_6H_4$	48	86	99:1
5	**6d**, $R^2 = 4\text{-}ClC_6H_4$	96	50	97:3
6	**6e**	48	82	62:38
7	**6f**	48	65(90)[d]	98:2
8	**6g**	96	31(50)[d]	>99:<1
9[c]	**6g**	24	86	>99:<1

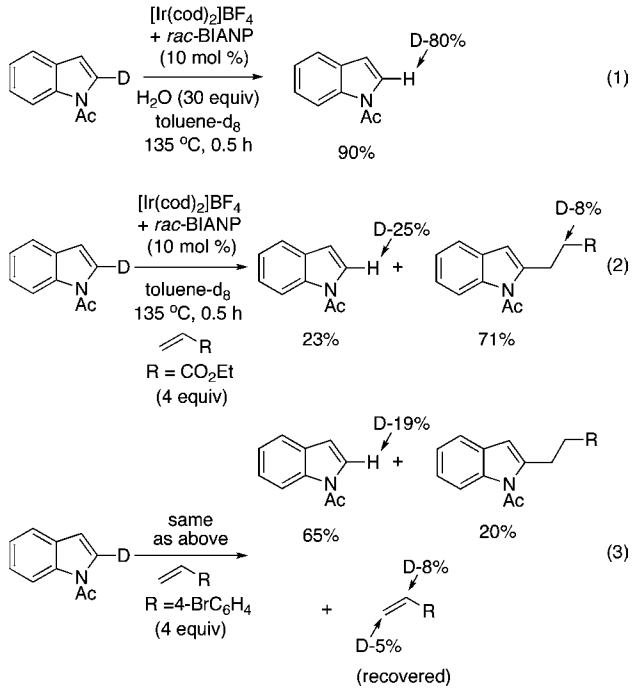
[a]Conditions: benzoylindole **5** (0.1 mmol), alkene **2** (0.4 mmol), $[Ir(cod)_2]BARF$ (0.01 mmol), (*R*)-SDP (0.01 mmol), dioxane (0.2 mL), unless otherwise noted. [b]The ratio of branch to linear product was determined by ^1H NMR. [c]1,1′-Bis(diphenylphosphino)ferrocene (DPPF, 10 mol %) was used as a ligand. [d]Isolated by GPC, the NMR yields were described in parentheses.

In the reaction of aliphatic alkenes, the branched product was predominant regardless of the directing group and the ligand of the Ir catalyst (Scheme 2). For example, the Ir-BINAP-catalyzed reaction of *N*-acetylindole with 1-nonene (**8**) gave the branched product **9** predominantly yet in low yield, because of low conversion. When a benzoyl group was used as a directing group, the products (**9b**/**10b**) were obtained in high yield with excellent selectivity under the same reaction conditions. The Ir-SDP catalyst realized almost perfect branched selectivity, but the yield was low.

Scheme 2. Reaction of *N*-Substituted Indoles with 1-Nonene

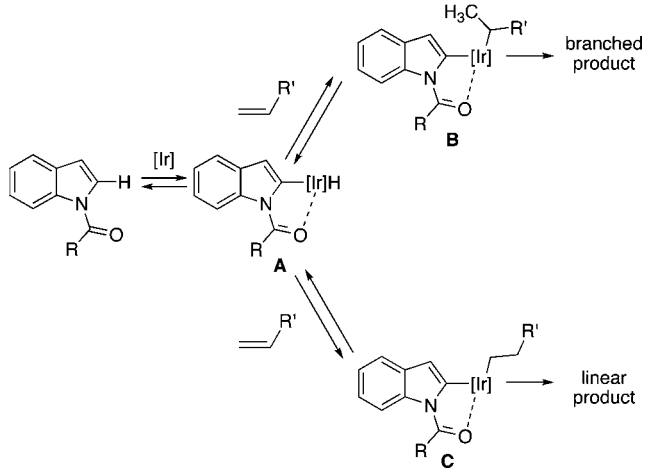


For a preliminary mechanistic study, we used 2-deuterated *N*-acetylindole-d_1: the reaction was examined in the absence of alkenes, but in the presence of H_2O (eq 1). As a result, the D content of the recovered substrate was 80%, and H/D exchange was ascertained. The present result implies that the sp^2 C−H bond at the C2-position of indole was cleaved under the present conditions. Next, the reactions of 2-deuterated *N*-acetylindole-d_1 with acrylate and 4-bromostyrene were examined (eqs 2 and 3). The D contents of the recovered substrates were different. Moreover, the incorporation of deuterium at both the α- and β-positions of recovered 4-bromostyrene was ascertained. These results indicate that C−H bond cleavage and alkene insertion are reversible.



On the basis of the above labeling experiments, we propose the following mechanism (Scheme 3). Cleavage of the C−H bond at the C2-position of *N*-substituted indole gives the intermediate **A**.[14] Subsequent hydroiridation to alkene provides intermediates **B** and/or **C**.[15] Finally, reductive elimination gives alkylated branched and/or linear products. In the reaction of *N*-acetylindole with alkenes, intermediate **C** is more favorable than intermediate **B**. In contrast, with *N*-benzoylindole, intermediate **B** is more favorable.

Scheme 3. Plausible Reaction Mechanism



In conclusion, we have developed a cationic Ir(I)-catalyzed direct C2-alkylation of *N*-substituted indoles with alkenes via C−H bond functionalization, which selectively gives linear or

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branched 2-alkylindole in high to excellent selectivity. The selectivity of linear or branched product was controlled by the directing group and ligand. The present results constitute a new example of C2-alkylation of indoles. Further studies on the scope of the substrates, applications, and the precise mechanism are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The experimental procedure, NMR experiments, and physical properties of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) The Ir-DPPF catalyst generally realized a high yield and branched selectivity. The results were listed in the Supporting Information.

(14) By the stoichiometric reaction of *N*-acetylindole (**1b**) with Ir-*rac*-BINAP in an NMR tube, a small peak for M–H (−20.13 ppm) was observed by ^{1}H NMR, but the intermediate could not be characterized yet.

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