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Ir-Catalyzed Regio- and Enantioselective Friedel–Crafts-Type Allylic Alkylation of Indoles

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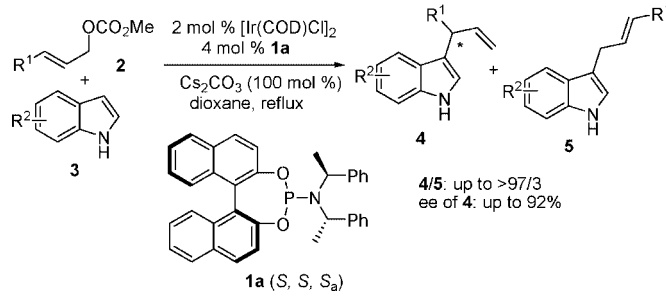
ABSTRACT



Highly regio- and enantioselective Ir-catalyzed Friedel–Crafts type allylic alkylation of indoles have been realized using [Ir(COD)Cl]$_2$/phosphoramidite ligand 1a, affording the branched products with up to >97/3 branched-linear ratio and 92% ee.

Synthesis of enantiopure indole derivatives is of significant importance because of the wide distribution of indole moieties in biologically active natural products and pharmaceutical compounds.[1] The enantioselective Friedel–Crafts reactions of indoles have attracted considerable interest and witnessed significant progress in the past decade.[2,3] Recently, transition-metal-catalyzed allylic alkylation has been proven suitable for direct indole functionalization.[4–6]

In 1999, Kočovský and co-workers reported the first allylic alkylation of indole with allyl acetates in the presence of a Mo(II) catalyst.[5a] Recently, Pd-catalyzed allylic alkylation of indole with allylic carbonates and the related intramolecular enantioselective alkylation have been carried out by Bandini and co-workers.[5b,c] A recent study by Chan and co-workers showed that high enantioselectivities were obtained during the alkylation of indoles with 1,3-diphenyl-2-propenyl acetate.[5e] Pd-catalyzed C-3 allylation of 3-substituted indole using trialkylborane and allyl alcohol have also been realized to afford 3,3-disubstituted indolenines and indolines.[6] Nev-

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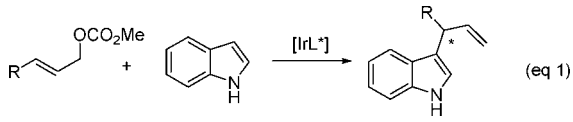
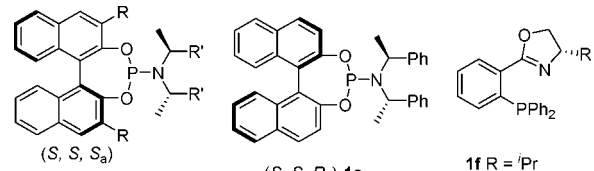
ertheless, transition-metal-catalyzed asymmetric allylic alkylation of indoles exhibit excellent potential for the synthesis of optically pure indole derivatives but the studies in this field remain quite limited. To the best of our knowledge, iridium catalyst[7,8] has not been utilized in this type of reaction, and neither has the 1,3-unsymmetrical allylic substrate.[9] However, the preferred branched alkylation product from the above reaction would lead to the product bearing a terminal alkene which would highly increase the utility of the alkylation product (eq 1).



(eq 1)

Due to our interest in both the Friedel–Crafts reaction of indole[10] and the Ir-catalyzed allylic alkylation reaction,[11] we envisaged that enantiopure indole derivatives bearing a terminal alkene moiety might be achieved through an Ir-catalyzed regio- and enantioselective Friedel–Crafts type allylic alkylation of indole. In this paper, we will report our preliminary results from the study on this subject.

At the outset, we utilized a well-developed Ir-catalytic system including $[Ir(COD)Cl]_2$ and a phosphoramidite **1a** (Figure 1) as the catalyst. In the presence of 2 mol % of $[Ir(COD)Cl]_2$, 4 mol % of **1a**, and 1 equiv of DBU, reaction of indole (**3a**, 200 mol %) and allyl carbonate **2a** in THF for 60 h only gave alkylation product **4aa** in 29% yield (entry 1, Table 1). To our delight, only branched alkylation product was detected by ^{1}H NMR of the crude



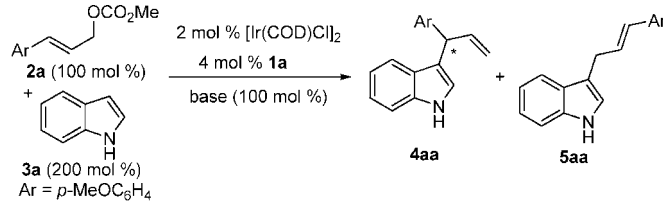
1a R = H, R' = Ph
1b R = H, R' = 2-Naphthyl
1c R = H, R' = 2-MeO-C_6H_4
1d R = Ph, R' = Ph

Figure 1. Chiral ligands **1a**−**g**.

reaction mixture. Examination of various bases such as DBU, Proton Sponge, NaOMe, and Cs_2CO_3 disclosed that Cs_2CO_3 was the optimal base, affording the branched product **4aa** in 60% yield with 93% ee (entries 1–6, Table 1). Changing the substrate ratio of **2a**/**3a** to 1/1 or 2/1 resulted in decreases of yield and ee in both cases (entries 7–8, Table 1). Varying different solvents such as toluene, dioxane, CH_2Cl_2, DMF, DME, CH_3CN, and reaction temperatures showed that reaction in refluxed dioxane gave the best result, affording **4aa** in 82% yield and 92% ee (entries 9–15, Table 1). Notably, running the reaction in toluene at 60 °C or in refluxed CH_2Cl_2 could also give **4aa** with excellent ee (92%) in slightly lower yields, 57% or 74%, respectively.

Next, we examined the effects of different chiral ligands, and the results are summarized in Table 2. Phosphoramidite ligands **1b** and **1c**, varying the substituents on the amine

Table 1. Optimization of the Reaction Conditions for Ir-Catalyzed Allylic Alkylation with Ligand **1a**[a]



entry	solvent	base	time (h)	T (°C)	yield[b] (%)	**4aa/5aa**[c]	ee[d] (%)
1	THF	DBU	60	reflux	29	>97/3	
2	THF	DABCO	60	reflux	8	73/27	
3	THF	Proton Sponge	60	reflux	trace		
4	THF	NaOMe	36	reflux	46	94/6	83
5	THF	Li_2CO_3	36	reflux	NR		
6	THF	Cs_2CO_3	21	reflux	60	>97/3	93
7[e]	THF	Cs_2CO_3	36	reflux	31	>97/3	88
8[f]	THF	Cs_2CO_3	36	reflux	45	>97/3	69
9	toluene	Cs_2CO_3	36	60	57	>97/3	92
10	dioxane	Cs_2CO_3	36	100	61	>97/3	93
11	dioxane	Cs_2CO_3	4	reflux	82	>97/3	92
12	CH_2Cl_2	Cs_2CO_3	20	reflux	74	>97/3	92
13	DMF	Cs_2CO_3	72	60	trace		
14	DME	Cs_2CO_3	84	60	33	80/20	89
15	CH_3CN	Cs_2CO_3	36	60	46	91/9	65

[a] Reaction conditions: 2 mol % of $[Ir(COD)Cl]_2$, 4 mol % of **1a**, 100 mol % of base, 200 mol % of **3a**. [b] Isolated yields. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] ee of **4aa** was determined by chiral HPLC analysis (Chiralcel OD-H). [e] **2a**/**3a** 1/1. [f] **2a**/**3a** 2/1.

Table 2. Screening of the Chiral Ligands[a]

entry	ligand	t (h)	yield[b] (%)	**4aa/5aa**[c]	ee[d] (%)
1	**1a**	4	82	>97/3	92
2	**1b**	8	81	>97/3	90
3	**1c**	17	75	>97/3	86
4	**1d**	24	trace		
5	**1e**	16	61	>97/3	63
6	**1f**	21	36	55/45	42
7	**1g**	21	NR		

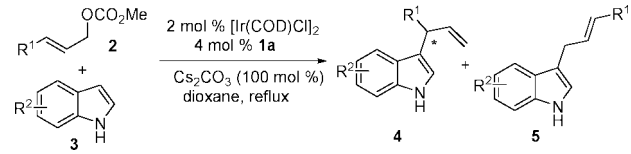
[a] Reactions were conducted under the conditions of entry 11, Table 1. [b] Isolated yields. [c] Determined by ^{1}H NMR of the crude reaction mixture [d] ee of **4aa** was determined by chiral HPLC analysis (Chiralcel OD-H).

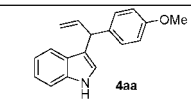
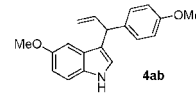
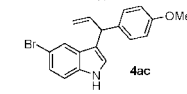
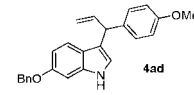
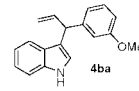
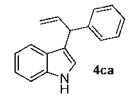
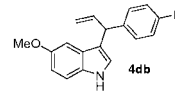
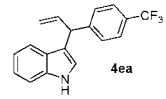
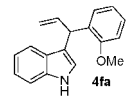
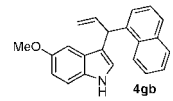
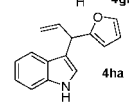
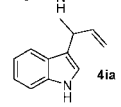
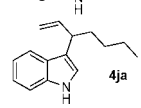
moiety, afforded the products in slightly lower yields and enantioselectivities (entries 1–3, Table 2). Ligand **1d** bearing phenyl groups on the 3,3′-positions of the binaphthyl scaffold was not effective for the reaction (entry 4, Table 2). The catalyst derived from **1e**, the diastereoisomer of **1a**, could catalyze the reaction in a lower yield and enantioselectivity (61% yield, 63% ee, entry 5, Table 2). PHOX ligands such as **1f** and **1g** were also tested, and **1f** was capable of catalyzing the reaction but in only 36% yield with 55/45 branched to linear ratio and 42% ee (entry 6, Table 2). Unfortunately, no reaction occurred when **1g** was employed as the ligand (entry 7, Table 2).

In the presence of 2 mol % of $[Ir(COD)Cl]_2$, 4 mol % of **1a**, and 1 equiv of Cs_2CO_3 in refluxed dioxane, alkylation of different indoles with various substituted allyl carbonates was carried out to test the generality of the reaction. As summarized in Table 3, alkylation of different indoles bearing either an electron-donating group (5-OMe, 6-OBn) or electron-withdrawing group (5-Br) with *p*-methoxyphenyl-substituted allyl carbonate **2a** all led to their corresponding alkylation products in good yields with excellent ee (72–85% yield, 85–92% ee, entries 1–4, Table 3). For the aryl allyl carbonate substrates, substituents having different electronic properties on the phenyl ring were well tolerated, and excellent enantioselectivities (85–92% ee, entries 4–8, Table 3) were obtained except for *o*-methoxyphenyl substrate **2f** (**4fa**, 84% yield, 70% ee, entry 9, Table 3).

The unfavorable ortho substituent effect can also be found during the reaction of 1-naphthyl-substituted allyl carbonate

Table 3. Ir-Catalyzed Allylic Alkylation of Indoles[a]



entry	product	t (h)	yield (%)[b]	**4**/**5**[c]	ee (%)[d]
1	 **4aa**	4	82	>97/3	92
2	 **4ab**	8	85	>97/3	89
3	 **4ac**	2	72	>97/3	91
4	 **4ad**	6	83	>97/3	85
5	 **4ba**	3	73	>97/3	91
6	 **4ca**	3	49	>97/3	85[e]
7	 **4db**	4	47[f]	>97/3	92
8	 **4ea**	3	63	>97/3	87
9	 **4fa**	3	84	>97/3	70
10	 **4gb**	5	39	>97/3	31
11	 **4ha**	3	80	>97/3	89
12	 **4ia**	4	43	93/7	88
13	 **4ja**	4	55	87/13	85

[a] Reaction conditions: 2 mol % of $[Ir(COD)Cl]_2$, 4 mol % of **1a**, 100 mol % of Cs_2CO_3, 200 mol % of **3** in refluxed dioxane. [b] Isolated yields. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] ee of **4** was determined by chiral HPLC analysis. [e] Determined by chiral HPLC of the *N*-Cbz derivative of **4ca**. [f] The yield was determined by ^{1}H NMR after column chromatography since the product is inseparable from the indole starting material.

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with 5-methoxy indole, and the product **4gb** was only obtained in 39% yield with 31% ee (entry 10, Table 3).

Notably, the reaction of 2-furyl-substituted allyl carbonate with indole proceeded smoothly to afford the desired product **4ha** in 80% yield with 89% ee (entry 11, Table 3). Under these same conditions, two carbonate substrates **2i** and **2j** derived from γ-alkylallyl alcohols have also been tested. Both of the substrates were tolerated but gave the alkylation products in slightly lower yields and regioselectivities (**4ia**, 43% yield, b/l 93/7, 88% ee; **4ja**, 55% yield, b/l 87/13, 85% ee; entries 11–12, Table 3).

In summary, we have found that $[Ir(COD)Cl]_2$/phosphoramidite ligand is an efficient catalytic system for the highly regio- and enantioselective Friedel–Crafts allylic alkylation of indoles. For various unsymmetrically allylic substrates and indoles, the reaction proceeded smoothly with excellent regioselectivities to afford the branched alkylation products with high ee. The ready availability of the starting materials and the great importance of the enantiopure products make the current methodology particularly interesting in organic synthesis. Further extending the reaction scope and developing more efficient catalytic systems are currently underway in our laboratory.

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Supporting Information Available: Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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