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Synthetic Methods

Regio- and Enantioselective Synthesis of *N*-Allylindoles by Iridium-Catalyzed Allylic Amination/Transition-Metal-Catalyzed Cyclization Reactions

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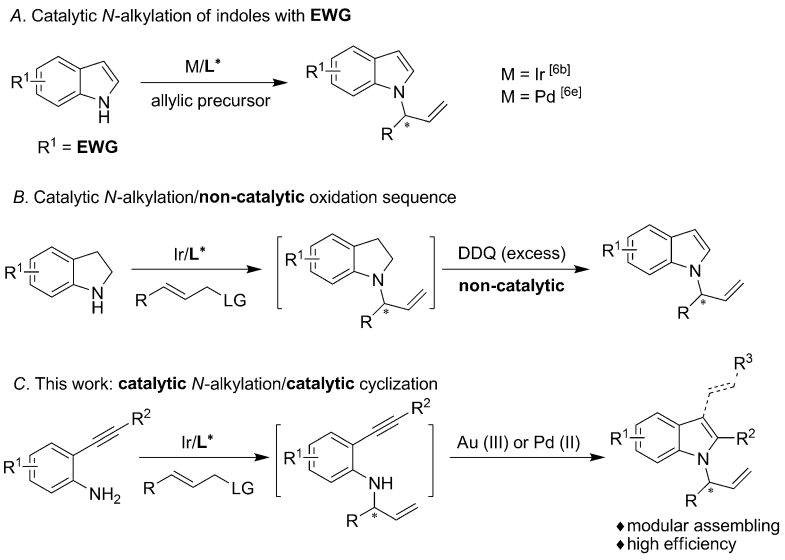
Abstract: Regio- and enantioselective synthesis of *N*-allylindoles was realized through an iridium-catalyzed asymmetric allylic amination reaction with 2-alkynylanilines and subsequent transition-metal-catalyzed cyclization reactions. The highly enantioenriched allylic amines prepared from Ir-catalysis were treated with catalytic amount of $NaAuCl_4 \cdot 2H_2O$ or $PdCl_2$ providing various substituted *N*-allylindoles in excellent yields and enantioselectivities.

Enantioenriched N-alkylated indole is a privileged structural motif embedded in a large number of natural and unnatural compounds.[1] However, among various catalytic asymmetric functionalizations of indole,[2] *N*-alkylation[3] of indole has been less developed compared with the well-established asymmetric reactions at the indolyl C3[4] (or C2[5]) position due to the high nucleophilicity of the C3 position and the weak acidity of the NH group of indoles. By introducing an electron-withdrawing group (EWG) on the indole core, the proton on the nitrogen atom becomes more acidic thus making the NH prone to alkylation.[6] This strategy has been successfully utilized by Hartwig[6b] and Trost[6e] with Ir and Pd catalysis, respectively (Scheme 1 A). Another approach towards chiral *N*-allylindoles is the stepwise *N*-alkylation of indoline and subsequent oxidation sequence (Scheme 1 B).[7] Despite its good compatibility of electronically diverse substrates, an excess amount of oxidant (2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DDQ) is needed to oxidize the corresponding indoline to indole. Therefore, it is extremely desirable to develop a catalytic asymmetric protocol to access optically active *N*-alkylated indoles with broad substrate scope in an atom-economical pathway.

As part of our ongoing programs towards Ir-catalyzed allylic substitution reactions,[8] we envisaged that *N*-allylindoles could be accessed through an Ir-catalyzed allylic amination reaction[9,10] with *ortho*-alkynylanilines and subsequent transition-metal-catalyzed cyclization reactions[11] (Scheme 1 C). This strategy merits from modular synthesis of enantioenriched *N*-allylindoles by incorporating diverse substituents that are not easily accessed either from indoles or indolines with the existing methods. Notably, Bandini and coworkers recently reported an elegant enantioselective gold-catalyzed cascade sequence to access substituted oxazino-indoles from *ortho*-alkynylaniline diols[12]. Herein, we report an efficient synthesis of enantioenriched *N*-allylindoles by the sequential iridium-catalyzed asymmetric allylic amination and transition-metal-catalyzed cyclization reactions.



Scheme 1. Methods for the synthesis of enantioenriched *N*-allylindoles.

We began our studies on the Ir-catalyzed allylic amination reaction by utilizing 2-(phenylethynyl)aniline (**1a**) and cinnamyl methyl carbonate (**2a**) as the model substrates. The results are summarized in Table 1. In the presence of 2 mol% of [Ir-

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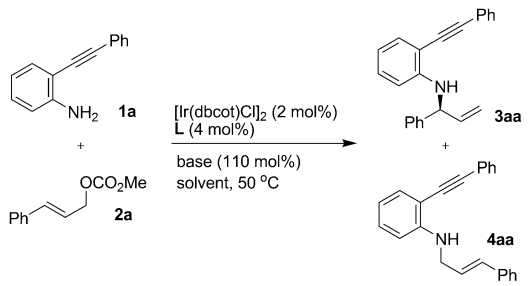
Table 1. Optimization of the reaction conditions.[a]



Entry	Ligand	Solvent	Base	Yield [%][b]	**3aa**/**4aa**[c]	*ee* [%][d]
1[e]	**L1**	THF	K_3PO_4	22	95:5	94
2	**L3**	THF	K_3PO_4	77	>97:3	99
3	**L3**	THF	Cs_2CO_3	78	97:3	97
4	**L3**	THF	Li_2CO_3	62	92:8	95
5	**L3**	THF	NaOEt	75	97:3	98
6	**L3**	THF	DABCO	29	>97:3	95
7	**L3**	THF	DBU	40	>97:3	96
8	**L3**	THF	DIEA	79	97:3	96
9	**L3**	THF	Et_3N	98	97:3	96
10	**L3**	THF	–	77	94:6	94
11	**L3**	CH_2Cl_2	Et_3N	97	>97:3	98
12	**L3**	Et_2O	Et_3N	97	96:4	98
13	**L3**	toluene	Et_3N	83	96:4	98
14	**L3**	dioxane	Et_3N	88	97:3	91
15	**L3**	MeCN	Et_3N	96	>97:3	98
16	**L1**	CH_2Cl_2	Et_3N	23	>97:3	92
17	**L2**	CH_2Cl_2	Et_3N	20	>97:3	94
18	**L4**	CH_2Cl_2	Et_3N	82	91:9	60
19	**L5**	CH_2Cl_2	Et_3N	62	87:13	87

[a] Reaction conditions: $[Ir(dbcot)Cl]_2$/**L**/**1a**/**2a**/base = 0.02:0.04:1.0:1.1:1.1, 0.1 M of **1a** at 50 °C. Catalyst was prepared through *n*-$PrNH_2$ activation. [b] Isolated yield of **3aa** and **4aa**. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis. [e] $[Ir(cod)Cl]_2$ was used instead of $[Ir(dbcot)Cl]_2$.

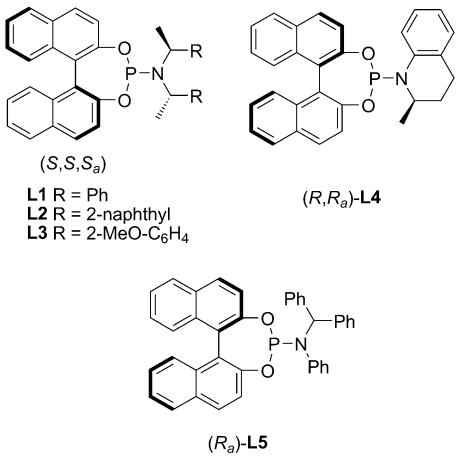


Figure 1. Chiral phosphoramidite ligands used in this work.

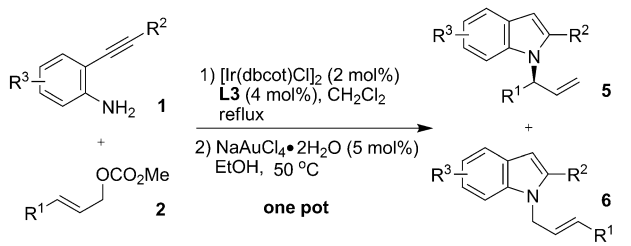
$(cod)Cl]_2$, 4 mol% of **L1** (Figure 1) and 110 mol% of K_3PO_4, the reaction in THF at 50 °C afforded the amination products in low yield, but with excellent selectivities (22% yield, branched/linear 95:5, 94% *ee*, entry 1, Table 1). To our delight, $[Ir(dbcot)Cl]_2$ (dbcot = dibenzo[*a*,*e*]cyclooctatetraene), introduced by Helmchen and coworkers[13] in Ir-catalyzed allylic substitution reactions, together with Alexakis ligand **L3**[14] exhibited excellent reactivity and selectivities (77% yield, branched/linear >97:3, 99% *ee*, entry 2, Table 1). With the Ir-catalyst generated in situ from 2 mol% of $[Ir(dbcot)Cl]_2$ and 4 mol% of **L3** in THF at 50 °C, examination of bases disclosed that all tested ones afforded excellent regioselectivity and enantioselectivity (entries 2–9, Table 1). Et_3N was found as the best base in terms of yield, regioselectivity and enantioselectivity (98% yield, branched/linear >97:3, 96% *ee*, entry 9, Table 1). Notably, excellent enantioselectivity could also be obtained in the reaction without external base, but the yield was dramatically decreased (entry 10, Table 1). Various solvents (CH_2Cl_2, Et_2O, toluene, dioxane, and MeCN) were compatible and CH_2Cl_2 was found to be the best one (97% yield, branched/linear 97:3, 98% *ee*, entry 11, Table 1). Finally, among several readily available chiral phosphoramidites tested, **L3** was found to be the optimal one (entries 11, 16–19, Table 1).

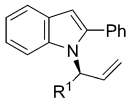
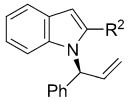
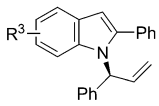
With the optimal conditions of Ir-catalyzed allylic amination reaction, we next investigated the transition-metal-catalyzed cyclization reaction. When $NaAuCl_4 \cdot 2H_2O$[15] was used, the desired *N*-allylindole was obtained exclusively and no *N*-allyl group migration occurred.[16] Further attempts to perform the amination and subsequent cyclization reactions in one-pot proved to be successful. Therefore, the regio- and enantioselective synthesis of *N*-allylindoles by Ir-catalyzed allylic amination/Au-catalyzed cylization reactions was realized as the following: upon the completion of the Ir-catalyzed enantioselective allylic amination reaction, the solvents were evaporated in vacuo and then $NaAuCl_4 \cdot 2H_2O$ and EtOH were added.

Under these above conditions, the substrate scope of *N*-allylindoles by Ir/Au catalysis was explored. The results are summarized in Table 2. With respect to allylic precursors, aryl and alkyl substituted allylic methyl carbonates were well tolerated providing *N*-allylindoles in good yields (67–95%) and enantioselectivities (92–98% *ee*, entries 1–8, Table 2). Various *o*-substituted alkynylanilines with aryl, heteroaryl, alkyl substituents on the alkynyl moiety also afforded good results (entries 9–13, Table 2). For alkynylaniline bearing 1-*c*-hexenyl substituent, excellent *ee* was also maintained albeit with a moderate yield and decreased regioselectivity (entry 14, Table 2). It is worth to mention that the TMS group on the alkynyl moiety can be efficiently removed during the Au-catalyzed cyclization reaction step[17] providing the *N*-allylindole with an H atom at the indolyl C2 position (entry 15, Table 2). Substrates bearing substituents (4-Me, 4-Cl) on the aromatic ring of anilines also performed well leading to the corresponding *N*-allylindoles in excellent yields, regio- and enantioselectivities (entries 16 and 17, Table 2).

The above Ir/Au catalysis provides the enantioenriched 2-substituted *N*-allylindoles by a one-pot procedure. Next, we turned our attention to develop a straightforward sequence to access the enantioenriched *N*-allylindoles bearing the variations at both the indolyl C3 and C2 positions. Though the access to C3 substituted indoles from the cyclization of *o*-alkynylanilines has been well studied,[18] the synthesis of C3 func-

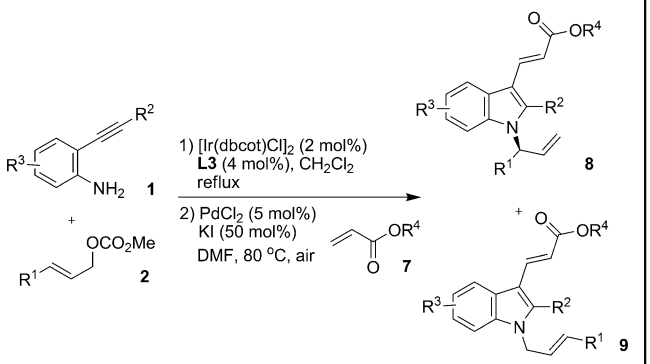
Table 2. Ir-catalyzed allylic amination and subsequent Au-catalyzed cyclization reactions.[a]

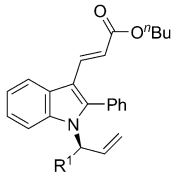
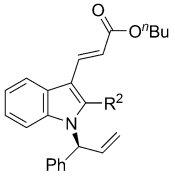
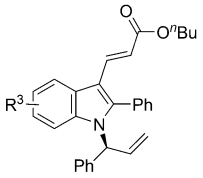
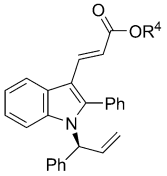


Entry	Product	Yield [%][b]	5/6[c]	*ee* [%][d]
				
1	**5aa:** R^1 = Ph	85	> 97:3	97
2	**5ab:** R^1 = 4-MeC_6H_4	95	> 97:3	98
3	**5ac:** R^1 = 4-BrC_6H_4	94	> 97:3	96
4	**5ad:** R^1 = 4-ClC_6H_4	76	> 97:3	96
5	**5ae:** R^1 = 3-$CF_3C_6H_4$	94	> 97:3	96
6	**5af:** R^1 = 3-ClC_6H_4	95	95:5	96
7	**5ag:** R^1 = Et	86	97:3	93
8	**5ah:** R^1 = *c*Pr	67	> 97:3	92
				
9	**5ba:** R^2 = 4-MeOC_6H_4	94	94:6	98
10	**5ca:** R^2 = 4-BrC_6H_4	81	94:6	96
11	**5da:** R^2 = 4-ClC_6H_4	92	97:3	99
12	**5ea:** R^2 = 2-thienyl	84	96:4	98
13	**5fa:** R^2 = CH_2CH_2Ph	92	95:5	98
14	**5ga:** R^2 = 1-*c*-hexenyl	44	90:10	98
15[e]	**5ha:** R^2 = H	74	> 97:3	95
				
16	**5ia:** R^3 = 5-Me	82	94:6	98
17	**5ja:** R^3 = 5-Cl	92	96:4	97

[a] Reaction conditions: 1) $[Ir(dbcot)Cl]_2$/**L3**/**1**/**2**/Et_3N = 0.02:0.04:1.0:1.1:1.1, 0.1 M of **1** in CH_2Cl_2 at reflux. Catalyst was prepared through *n*-$PrNH_2$ activation. 2) $NaAuCl_4 \cdot 2H_2O$/**1** = 0.05:1.0, 0.1 M in EtOH at 50 °C. [b] Isolated yield of **5** and **6**. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis. [e] R^2 = TMS in the corresponding *o*-alkynylaniline.

Table 3. Ir-catalyzed allylic amination and subsequent Pd-catalyzed cyclization/Heck reactions.[a]



Entry	Product	Yield [%][b]	8/9[c]	*ee* [%][d]
				
1	**8aa:** R^1 = Ph	72	> 97:3	96
2	**8ab:** R^1 = 4-MeC_6H_4	65	> 97:3	97
3	**8ac:** R^1 = 4-BrC_6H_4	65	> 97:3	97
4	**8ad:** R^1 = Me	57	> 97:3	90
				
5	**8ae:** R^2 = 4-BrC_6H_4	65	> 97:3	97
6	**8af:** R^2 = 2-thienyl	60	96:4	96
7	**8ag:** R^2 = CH_2CH_2Ph	43	95:5	97
				
8	**8ah:** R^3 = 5-Me	69	94:6	98
9	**8ai:** R^3 = 5-Cl	47	96:4	92
				
10	**8aj:** R^4 = Me	71	> 97:3	96
11	**8ak:** R^4 = Et	72	> 97:3	98

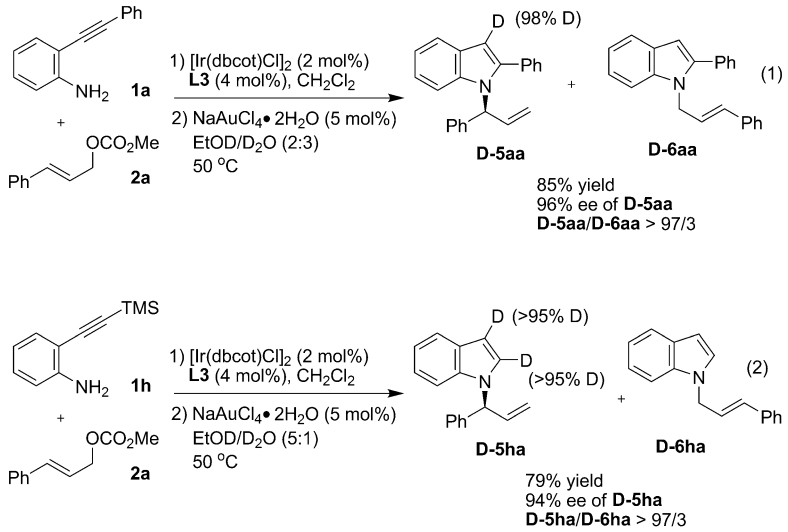
[a] Reaction conditions: 1) $[Ir(dbcot)Cl]_2$/**L3**/**1**/**2**/Et_3N = 0.02:0.04:1.0:1.1:1.1, 0.1 M of **1** in CH_2Cl_2 at reflux. Catalyst was prepared through *n*-$PrNH_2$ activation. 2) $PdCl_2$/KI/**1**/**7** = 0.05:0.5:1.0:6.0, 0.1 M in DMF at 80 °C. [b] Isolated yield of **8** and **9**. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis.

tionalized enantioenriched *N*-allylindoles remains rare. The enantioenriched *N*-allyl *ortho*-alkynylanilines were found to be good substrates in a cascade nucleopalladation/Heck reaction.[19] Upon the completion of the Ir-catalyzed enantioselective allylic amination reaction, the amination products obtained by short silica gel column chromatography were then subjected to a cascade nucleopalladation/Heck reaction in the presence of $PdCl_2$/KI/acrylates in DMF at 80 °C. Various *N*-allylindoles bearing an acrylate group at the indolyl C3 position were obtained in moderate to good yields with excellent regio- and enantioselectivities (Table 3). The reaction conditions were found to be compatible for all the substituted allyl carbonates and acrylates tested in our hands.

Deuterium-labeled compounds are widely used as internal standards in mass spectrometry or to elucidate the reaction mechanistic hypothesis.[20] The current method allows the

facile deuterium incorporation at the specific positions of enantioenriched *N*-allylindoles. By using EtOD/D_2O as the co-solvents in the gold-catalyzed cyclization reactions, enantioenriched *N*-allylindoles bearing high deuterium incorporations at the indolyl C3 position (**D-5 aa**, [Eq. 1]) or both the indolyl C2 and C3 positions (**D-5 ha**, [Eq. 2]) were obtained, respectively. It is very attractive to use the inexpensive and safe-to-handle EtOD/D_2O as the deuterium source of D-labeled highly enantioenriched *N*-allylindoles.

In summary, we have developed an efficient synthesis of enantioenriched substituted *N*-allylindoles by Ir-catalyzed asymmetric allylic amination reaction and subsequent transition-metal-catalyzed cyclization reactions. The current synthesis of enantioenriched *N*-allylindoles has several notable features: 1) broad substrate scope with high yields and *ee*; 2) modular synthesis of various substituted *N*-allylindole bearing diverse substituents; 3) compatible with one-pot procedure and cascade reaction.



Experimental Section

General procedure for one-pot synthesis of *N*-allylindoles by Ir-catalyzed allylic amination reaction and subsequent Au-catalyzed cyclization reactions

A flame-dried Schlenk tube was cooled to room temperature and filled with argon. To this flask were added $[Ir(dbcot)Cl]_2$ (3.5 mg, 0.004 mmol, 2 mol%), phosphoramidite ligand **L3** (4.8 mg, 0.008 mmol, 4 mol%), THF (0.5 mL) and *n*-propylamine (0.5 mL). The reaction mixture was heated at 50 °C for 0.5 h, and the color of the solution was changed from orange to light yellow. Then the reaction mixture was cooled to room temperature, and the solvents were removed in vacuo. To the same flask, *ortho*-alkynylaniline derivative **1** (0.20 mmol), allylic carbonate **2** (0.22 mmol), Et_3N (22.2 mg, 0.22 mmol) and THF (2 mL) were added. The reaction mixture was stirred at reflux for 24 h. After the reaction was complete (monitored by TLC), the solvents were evaporated in vacuo, $NaAuCl_4 \cdot 2H_2O$ (4.0 mg, 5 mol%) and EtOH (2 mL) were then added directly in the same tube. The reaction mixture was stirred at 50 °C for 3 h. After the reaction was complete (monitored by TLC), the crude reaction mixture was filtrated through Celite and washed with EtOAc. The solvents were removed under reduced pressure. Then the residue was purified by silica gel column chromatography to afford the products (eluent: petroleum ether/EtOAc = 100:1).

General procedure for the synthesis of 2,3-disubstituted *N*-allyl indoles by Ir-catalyzed allylic amination reaction/Pd-catalyzed cyclization and Heck reactions

Ir-catalyzed allylic amination reaction was carried out following the procedure described above. After the reaction was complete (monitored by TLC), the solvents were removed under reduced pressure. Then the residue was purified by silica gel column chromatography to afford the amination product. To a flask containing the amination product, $PdCl_2$ (1.8 mg, 0.01 mmol, 5 mol%), KI (16.6 mg, 0.1 mmol, 50 mol%), acrylate (1.2 mmol, 6.0 equiv) and DMF (2.0 mL) were added. The reaction mixture was stirred at 80 °C. After the reaction was complete (monitored by TLC), the crude reaction mixture was filtrated through celite and washed with EtOAc. The reaction mixture was washed twice with H_2O and then with brine. The organic phase was separated, dried over anhydrous Na_2SO_4, filtrated, and concentrated under reduced pressure. Then the residue was purified by silica gel column chromatography to afford the products (eluent: petroleum ether/EtOAc = 50:1).

Acknowledgements

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Keywords: allylic substitution · *N*-allylindole · asymmetric catalysis · enantioselectivity · iridium

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