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Catalytic Asymmetric Allylic Amination with Isatins, Sulfonamides, Imides, Amines, and *N*-Heterocycles

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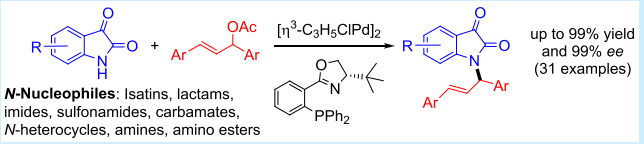
ABSTRACT: A generally useful palladium-catalyzed method for the asymmetric allylic amination with a large variety of isatins, sulfonamides, imides, amines, and *N*-heterocycles is introduced. A single protocol with a readily available catalyst accomplishes this reaction at room temperature with high yields and enantioselectivities often exceeding 90%, which is demonstrated with 31 examples.



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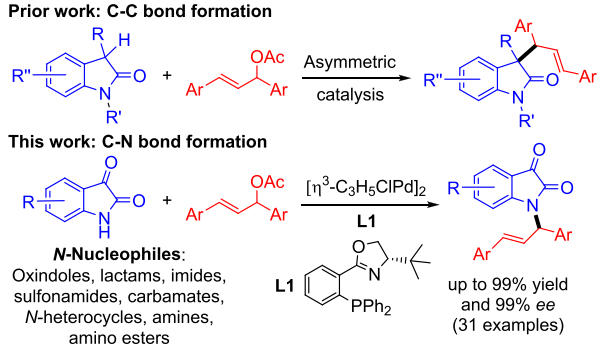
The transition-metal-catalyzed asymmetric allylic alkylation (AAA) has become a popular synthetic tool for the construction of multifunctional building blocks and biologically active compounds.[1] In comparison to the large variety of enantioselective carbon−carbon bond formations that have been achieved with this powerful reaction, relatively few examples with nitrogen nucleophiles have appeared in the literature (Scheme 1).[2] The frequent occurrence of the oxindole ring and derivatives thereof in alkaloids and the therapeutic potential in a wide range of medicinal applications have motivated the development of countless asymmetric carbon−carbon or carbon−heteroatom bond forming reactions that generate a chiral center at C-3 while the lactam nitrogen is typically protected and not exploited.[3]

Scheme 1. Asymmetric Allylic Alkylation with Oxindoles and Isatins



To the best of our knowledge, an enantioselective allylic amination method that utilizes oxindoles or isatins as *N*-nucleophiles has not been reported despite the medicinal value and the widespread presence of the indoline motif in natural compounds.[4] A literature search revealed a few examples of asymmetric carbon−nitrogen bond construction with oxindole or isatin *N*-nucleophiles. Liu and co-workers developed a protocol for diastereoselective *N*-glycosylation of unsaturated hexopyranosides with isatin which gives efficient access to both carbohydrate anomers.[5] Nakazaki described a palladium-catalyzed asymmetric intramolecular arylation procedure that affords axially chiral *N*-aryl oxindoles[6] and highly enantioselective organocatalytic aza-Michael additions of isatin derivatives to unsaturated diketones were reported by Kanger.[7] Based on the scarcity of catalytic asymmetric C−N bond formations with *N*-nucleophilic isatins and oxindoles, we decided to investigate the possibility of enantioselective allylic aminations with this important heterocyclic scaffold. We now wish to report the development of a method that accomplishes this task with high yields and enantioselectivities. In addition, we show that this chemistry is widely useful and applicable to amines, sulfonamides, imides, lactams, amino esters, carbamates, aromatic heterocycles, and other *N*-nucleophiles.

We began our search for an efficient asymmetric allylic amination protocol by screening the reaction between isatin, **1**, and 1,3-diphenylallyl acetate, **2**, in the presence 5 mol % of $[\eta^3\text{-}C_3H_5ClPd]_2$, 12 mol % of (*S*)-4-*tert*-butyl-2-[2-(diphenylphosphino)phenyl]-2-oxazoline and K_2CO_3 at 25 °C in various solvents (Table 1, entries 1−6). We found that the best results are obtained with chloroform affording **3** in 67% yield and 99% ee (Table 1, entry 6). We then tested a variety of organic and inorganic bases, but the yields did not improve (Table 1, entries 6−14). Comparison of the phoshinoxazolines **L1**, **L2**, and **L3**, SEGPHOS (**L4**), and the BINAP derivatives **L5** and **L6** showed that both yields and ee's varied considerably when these ligands were used. The phosphinoxazoline ligand, **L1**, however, gave superior results,

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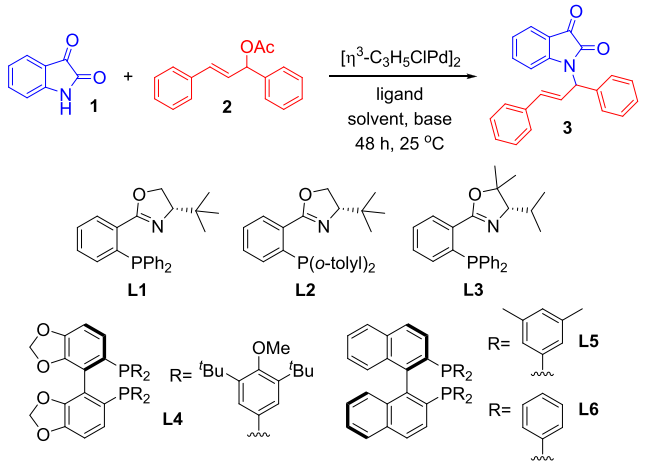
Table 1. Optimization of the Asymmetric Allylic Amination Using Isatin, 1, and Allylic Acetate 2[a]



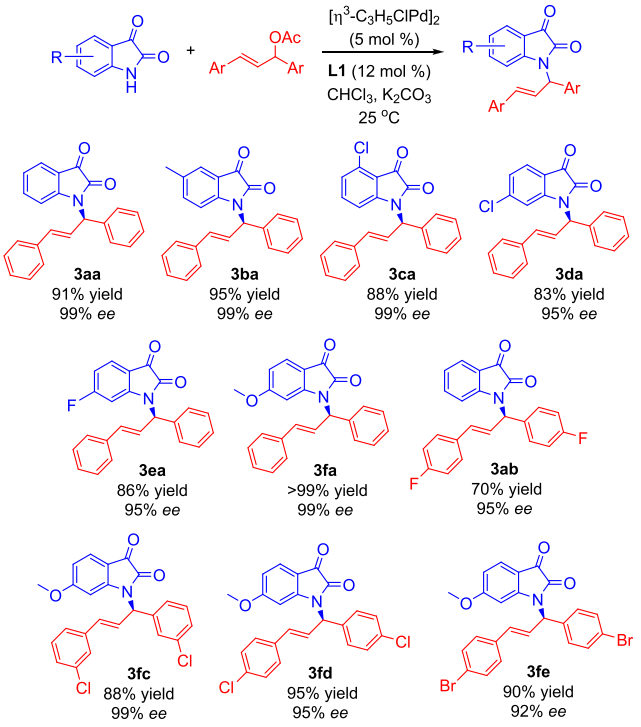
entry	solvent	base	ligand	yield[b] (%)	ee[c] (%)
1	THF	K_2CO_3	**L1**	28	99
2	DCM	K_2CO_3	**L1**	60	80
3	ACN	K_2CO_3	**L1**	37	32
4	1,4-dioxane	K_2CO_3	**L1**	27	0
5	DMF	K_2CO_3	**L1**	67	98
6	$CHCl_3$	K_2CO_3	**L1**	67	99
7	$CHCl_3$	Na_2CO_3	**L1**	29	99
8	$CHCl_3$	K_3PO_4	**L1**	67	99
9	$CHCl_3$	KO^{t}Bu	**L1**	43	99
10	$CHCl_3$	Cs_2CO_3	**L1**	46	99
11	$CHCl_3$	BSA:KOAc[e]	**L1**	50	99
12	$CHCl_3$	DBU	**L1**	17	98
13	$CHCl_3$	DIPEA	**L1**	43	37
14	$CHCl_3$	Et_3N	**L1**	44	51
15	$CHCl_3$	K_2CO_3	**L1**	67	99
16	$CHCl_3$	K_2CO_3	**L2**	46	91
17	$CHCl_3$	K_2CO_3	**L3**	45	90
18	$CHCl_3$	K_2CO_3	**L4**	31	93
19	$CHCl_3$	K_2CO_3	**L5**	74	81
20	$CHCl_3$	K_2CO_3	**L6**	63	94
21[d]	$CHCl_3$	K_2CO_3	**L1**	91	99

[a]Reactions were carried out with **1** (0.2 mmol) and **2** (0.2 mmol) at 25 °C for 48 h under inert atmosphere using 5 mol % of the Pd complex and 12 mol % of the chiral ligand. [b]Isolated yield. [c]ee values were determined using a ChiralPak IA column and 95:5 hexanes/IPA as mobile phase. [d]Acetate/isatin (2:1). [e]BSA/KOAc (3:1).

and we found that **3** is produced in 91% yield and 99% ee when 2 equiv of the allylic acetate are employed (Table 1, entry 21). Interestingly, **3** was formed in only 37% yield from the corrresponding allylic *tert*-butyl carbonate under the same conditions.

With an optimized protocol in hand, we continued with the evaluation of the isatin substrate scope. We found that a variety of substituted isatins carrying halogen, alkyl, and alkoxy groups undergo C−N bond formation with high yields ranging from 83 to 99% and remarkable 95−99% ee (Scheme 2). For example, (*R*,*E*)-1-(1,3-diphenylallyl)-5-methylindoline-2,3-dione, **3ba**, was isolated in 95% yield and 99% ee, and the 4-chloroisatin analogue **3ca** was obtained in 88% yield and 99% ee. It is noteworthy that the reaction with 6-methoxyisatin gave **3fa** in quantitative yield and 99% ee. Substituted 1,3-diphenylallyl acetates carrying halogens in the *meta* and *para*

Scheme 2. Substrate Scope of the Palladium-Catalyzed C−N Bond Formation between Isatins and 1,3-Diarylallyl Acetates[a]



[a]The absolute configuration was assigned based on analogy with the tetrazole **4la**.

positions reacted smoothly toward the corresponding amination products in 70−90% yield and up to 99% ee. C−N bond formation, however, was not observed when nitro-substituted 1,3-diphenylallyl acetates were employed in the optimized protocol. As mentioned above, isatins have not been used in asymmetric C−N bond formation with 1,3-diphenylallyl acetates, and to the best of our knowledge all products shown in Scheme 2 have not been reported to date.

We were pleased to find that our method can also be applied to imides, amides, 3,3-disubstituted oxindoles, and sulfonamides (Scheme 3). Essentially the same procedure was used without additional optimization and the desired products were obtained in 67−99% and with enantioselectivities ranging from 94 to 99% ee. The imides **4aa** and **4ba**, which are both new compounds, were produced in quantitative yields and with literally perfect ee's. Excellent results were also observed with phthalimide, 3,3-difluoroxindole, and sulfonamides. We note that the imides may serve as an ammonia surrogate which would give practical access to chiral primary 1,3-diarylallyl amines.

Encouraged by the general success, we decided to investigate the possibility of C−N bond formation with several *N*-heterocycles (Scheme 4). The reactions with imidazole and benzimidazole occurred with high asymmetric induction producing **4ia** and **4ja** in 84% yield and 98% ee, and benzo[*d*]oxazol-2(3*H*)-one furnished **4ja** with a yield of 89% and 93% ee. Similar results were obtained with theophylline, triazole, and 1-methyluracil. Single crystals of the triazole **4la** suitable for X-ray analysis were grown by slow evaporation of a hexanes−dichloromethane (50:50 v/v) solution, and the absolute configuration was assigned as *R*.

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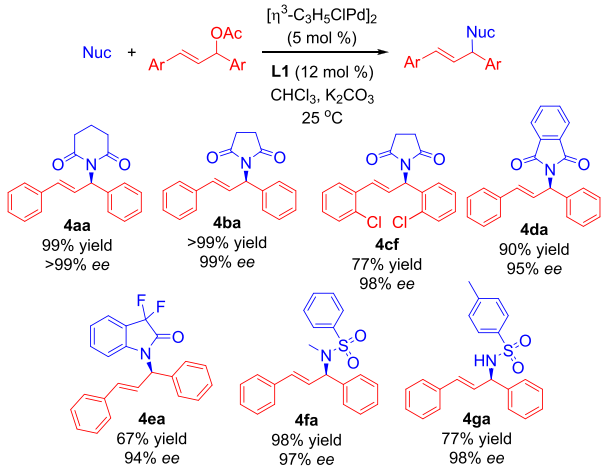
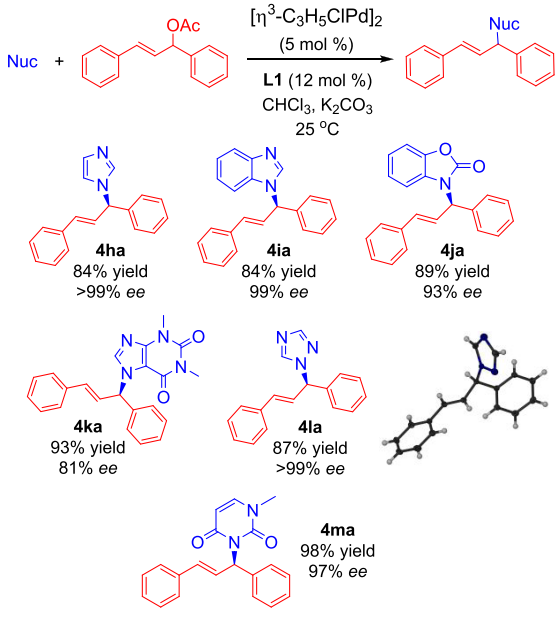
Scheme 3. Enantioselective Carbon−Nitrogen Bond Formation with Amides and Imides[a]



[a]The absolute configuration was assigned based on analogy with the tetrazole **4la**.

Scheme 4. Asymmetric Allylic Allylation with *N*-Heterocycles[a]

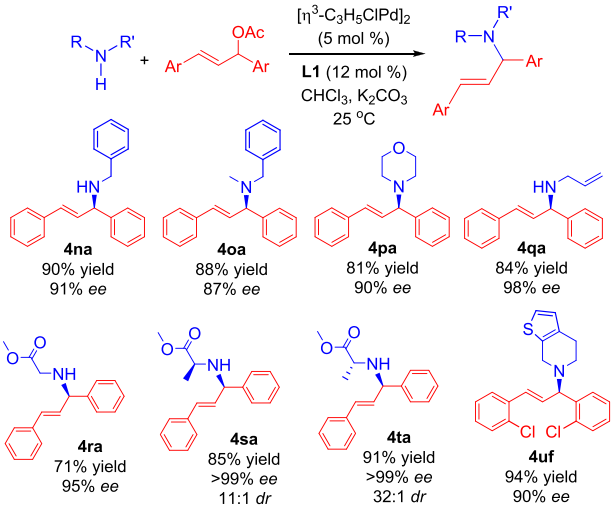


[a]The absolute configuration was assigned based on analogy with the tetrazole **4la**.

Finally, we examined amines and amino acid derivatives. Using benzylamine, *N*-methylbenzylamine, morpholine, and allylamine as substrates, **4na**, **4oa**, **4pa**, and **4qa** were synthesized in good yields and high ee's. The reaction with glycine methyl ester gave **4ra** in 71% yield and 99% ee, which compares well with previously reported results.[8] The diastereoselective C−N bond formation with alanine methyl esters revealed that high stereocontrol can be achieved with matched and mismatched pairs; both **4sa** and **4ta** were obtained from (*S*)- and (*R*)-alanine methyl ester in yields greater than 85% and with diastereomeric ratios of 11:1 and 32:1, respectively (Scheme 5).

In conclusion, we have developed an efficient method that allows asymmetric allylic C−N bond formation with high

Scheme 5. Extension of the Substrate Scope to Amines and Amino Acid Derivatives[a]



[a]The absolute configuration was assigned based on analogy with the tetrazole **4la**.

yields and enantioselectivities using a chiral palladium catalyst generated from commercially available $[\eta^3\text{-}C_3H_5ClPd]_2$ and 4-*tert*-butyl-2-[2-(diphenylphosphino)phenyl]-2-oxazoline and K_2CO_3 as base in chloroform at room temperature. A single protocol was successfully applied to isatins, sulfonamides, imides, amines and various *N*-heterocycles. The general usefulness was demonstrated with the synthesis of 31 allylic amination products, including 22 new structures, which were obtained in 67−99% yields and with enantioselectivities above 90% ee in most cases.

General Procedure

A mixture of (*S*)-4-*tert*-butyl-2-[2-(diphenylphosphino)-phenyl]-2-oxazoline (0.12 mmol, 12 mol %) and $[\eta^3\text{-}C_3H_5ClPd]_2$ (0.05 mmol, 5 mol %) in dry $CHCl_3$ (5.0 mL) was stirred at room temperature under N_2 atmosphere for 2 h. (*E*)-1,3-Diphenylallyl acetate (502.5 mg, 2.0 mmol) was added followed by 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (139.2 mg, 1.0 mmol) and potassium carbonate (276.5 mg, 2.0 mmol). The resulting mixture was stirred at room temperature for 4 days, and the reaction was monitored by TLC. The crude product was purified by flash chromatography on silica gel using 95:5 hexanes−ethyl acetate as the mobile phase. (*R*,*E*)-5-(1,3-Bis(2-chlorophenyl)allyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]-pyridine was obtained as an orange viscous oil in 90% yield (361.2 mg, 0.90 mmol). R_f = 0.71 (hexanes/EtOAc, 8:2). The enantiomeric excess was determined by HPLC (CHIRALPAK IA, hexanes/*i*-PrOH 98:2, flow rate 1 mL/min, λ = 254 nm) as 90% ee, t_R (minor) = 4.4 min, t_R (major) = 5.1 min. ^{1}H NMR (400 MHz, chloroform-*d*): δ = 7.75 (dd, J = 7.9, 1.8 Hz, 1H), 7.54−7.04 (m, 10H), 6.69 (d, J = 5.2 Hz, 1H), 6.20 (dd, J = 15.8, 9.0 Hz, 1H), 4.73 (d, J = 9.0 Hz, 1H), 3.76 (d, J = 14.6 Hz, 1H), 3.54 (d, J = 14.5 Hz, 1H), 2.93- 2.81 (m, 4H). ^{13}C NMR (100 MHz, chloroform-*d*): δ = 139.0, 134.8, 133.9, 133.8, 133.6, 133.1, 133.1, 129.8, 129.7, 129.0, 128.6, 128.2, 127.7, 127.4, 126.9, 126.8, 125.5, 122.7, 68.1, 51.8, 48.8, 25.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{19}Cl_2NSNa$ 400.0693, found 400.0687.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00936.

Detailed experimental procedures, compound characterization, NMR spectra, chiral HPLC chromatograms, and crystallographic information (PDF)

Accession Codes

CCDC 1983652 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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