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Synthesis of Enantiomerically Enriched 3-Amino-2-oxindoles through a Palladium-Mediated Asymmetric Intramolecular Arylation of α-Ketimino Amides

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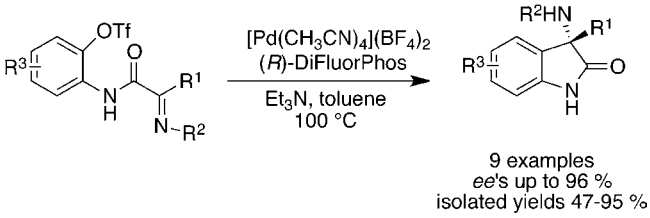
ABSTRACT



A highly efficient and enantioselective synthesis of 3-amino-2-oxindoles through a palladium-catalyzed asymmetric intramolecular arylation of α-ketimino amides using (*R*)-DiFluorPhos as the coordinating ligand is reported. This report constitutes the first enantioselective palladium-catalyzed arylation of ketimines.

Oxindoles bearing a tetrasubstituted carbon stereocenter at the 3-position are common motifs in natural products and in pharmaceutically interesting lead compounds.[1] Recently, 3-amino-2-oxindoles have been reported to be biologically active against a variety of targets including anxiety and depression (SSR149415)[2] as well as a gastrin/CCK-B receptor agonist (AG-041R)[3] and an antimalarial agent (NITD609)[4] (Figure 1). Although this subclass is clearly important, relatively few methods have been described to construct *enantiomerically enriched* 3-amino-2-oxindoles.[5] While the catalytic enantioselective α-amination of prochiral isatins catalyzed by chiral scandium complexes,[6] chiral Schiff base−nickel complexes,[7] and cinchona alkaloid analogs[8] have been reported to proceed with high enantioselectivity, further routes are needed to

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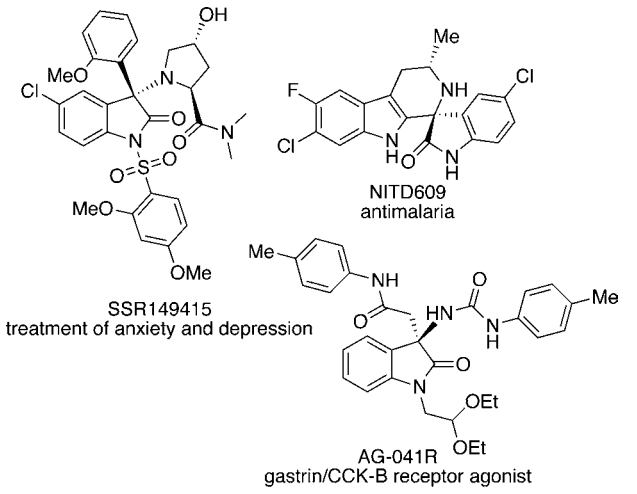


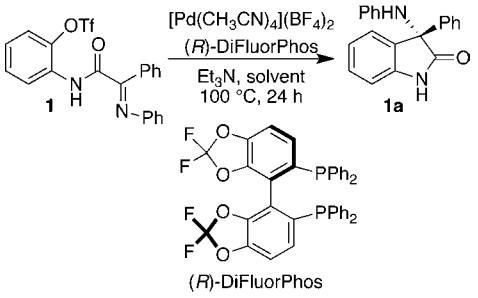
Figure 1. Pharmacologically active compounds based on the 3-amino-2-oxindole framework.

expand the synthetic repertoire leading to this compound series.

The first asymmetric palladium-catalyzed intramolecular coupling reaction to form enantioenriched oxindoles was reported in 1993 by Overman et al., who utilized the Heck reaction during their synthesis of (−)-physostigmine and (−)-physovenine.[9] A decade later Overman and co-workers expanded the substrate scope of this process to form a wide variety of enantioenriched 3-alkyl-3-aryloxindoles.[10] Subsequently this asymmetric Heck reaction has been applied to form an enantioenriched spirocyclic oxindole framework[11] in a tandem Heck−cyanation[12] combination process. The synthesis of oxindoles by asymmetric intramolecular palladium-catalyzed amide α-arylation was reported by Hartwig et al. in 2001 and was later improved further by several groups.[13] For example, Kündig reported the first intramolecular α-arylation of amides containing heteroatom substituents, which led to enantioenriched 3-alkoxy- and 3-amino-2-oxindoles.[14] This report demonstrates a catalytic asymmetric synthesis of 3-amino-2-oxindoles with four examples that are bearing substituents on the nitrogen atom. Recently, Shibasaki developed an approach to yield enantioenriched 3-hydroxy-2-oxindoles via an intramolecular arylation of α-keto amides to give cyclized products in high yields and enantioselectivities with a wide variety of substrates.[15]

Surprisingly, despite providing access to enantiomerically enriched chiral amines possessing an α-tetrasubstituted stereogenic center in one step, asymmetric transition-metal-catalyzed addition of organometallic reagents to ketimines has only received little attention by the synthetic community.[16] Nevertheless Kanai and Shibasaki have developed a copper-catalyzed asymmetric addition of allylboronates to ketimines[17] and similarly reported the asymmetric addition of dialkylzincs using copper[18] and zirconium[19] catalysis. Furthermore, Hayashi recently

Table 1. Optimization of Asymmetric Pd-Catalyzed Intramolecular Arylation of **1**[a]



entry	Pd (mol %)	Pd: ligand	solvent	conv[b] (yield) (%)	ee[c] (%)
1	5	1:1.2	CF_3-C_6H_5	<99 (83)	80
2	10	1:1.2	CF_3-C_6H_5	<99 (93)	**85**
3	2.5	1:1.2	CF_3-C_6H_5	<65 (56)	78
4	5	1:2	CF_3-C_6H_5	<99 (83)	**84**
5	10	1:1.2	toluene	<99 (95)	**86**
6	10	1:1.2	1,4-dioxane	<99 (90)	38
7	10	1:1.2	acetonitrile	<99 (76)	77
8[d]	5	1:1.2	CF_3-C_6H_5	60 (43)	72
9[e]	5	1:1.2	CF_3-C_6H_5	70 (63)	86

[a] Reaction conditions: 0.3 mmol of **1**, *X* mol % $[Pd(CH_3CN)_4](BF_4)_2$, *Y* mol % (*R*)-DiFluorPhos, 0.75 mmol of Et_3N, 0.5 mL of solvent, 100 °C, 24 h. [b] Determined by ^1H NMR. [c] Determined by chiral HPLC. See Supporting Information for absolute configuration determination. [d] $Pd(OAc)_2$ was used as a Pd source. [e] $Pd_2(dba)_3$ was used as a Pd source.

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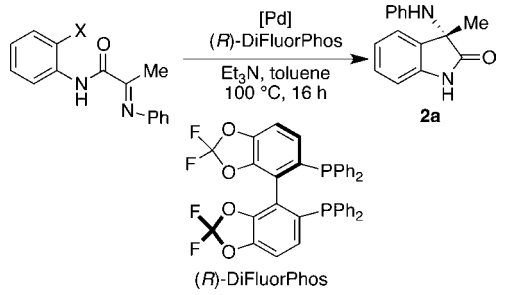
Table 2. Comparison of Aryl Triflate versus Aryl Iodide in the Asymmetric Pd-Catalyzed Arylation of **2**[a]



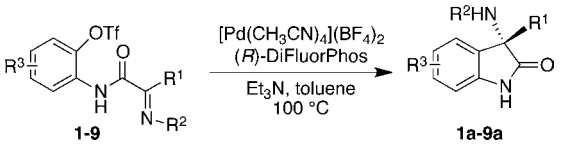
entry	X	Pd	conv[b] (%)	ee[c] (%)
1	OTf	$[Pd(CH_3CN)_4](BF_4)_2$	<99	85
2	I	$[Pd(CH_3CN)_4](BF_4)_2$	trace	n.d.
3	OTf	$Pd(P(o\text{-}Tol)_3)_2$	50	90
4	I	$Pd(P(o\text{-}Tol)_3)_2$	20	2
5[d]	I	$Pd(P(o\text{-}Tol)_3)_2$	90	35

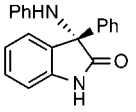
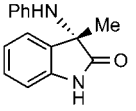
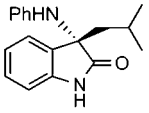
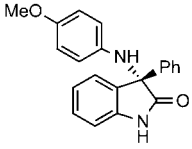
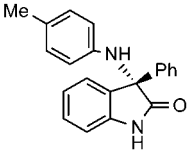
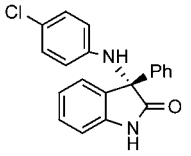
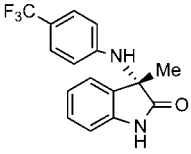
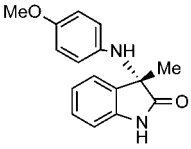
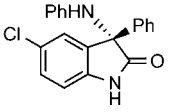
[a] Reaction conditions: 0.04 mmol of substrate, 10 mol % Pd-precursor, 20 mol % (*R*)-DiFluorPhos, 0.1 mmol of Et_3N, 0.5 mL of toluene, 100 °C, 16 h. [b] Determined by ^1H NMR. [c] Determined by chiral HPLC. [d] 0.04 mmol of AgOTf was added.

commented on a highly enantioselective rhodium-catalyzed arylation of *N*-tosyl ketimines.[20] Moreover, Cu-catalyzed addition of alkynes to isoquinoline iminium salt has been reported to yield products in high enantioselectivity.[21]

Considering the recent work on enantioselective palladium-catalyzed α-arylation of amides, we reasoned that α-ketimino amides would provide an interesting new substrate class for this transformation, which could potentially lead to enantiomerically enriched 3-amino-2-oxindoles with a high level of structural diversity. We decided therefore to use α-ketimino amide **1** derived from aniline as a substrate to screen the optimal reaction conditions for the enantioselective palladium-catalyzed intramolecular arylation (Table 1). The initial screening of the ligands showed that (*R*)-DiFluorPhos (86% *ee*, 95% yield) gave both the highest enantioselectivity and isolated yield as compared to (*R*)-BINAP (41% *ee*, 95% yield), (*S*)-Tol-BINAP (47% *ee*, 86% yield) and (*R*)-AvraPhos[22] (74% *ee*, 70% yield).[23] A chiral N,P chelating ligand, (*S*)-PHOX, afforded only traces of the desired cyclized product. Furthermore, we found that $[Pd(CH_3CN)_4](BF_4)_2$ as a source of palladium to be superior to $Pd(OAc)_2$ and $Pd_2(dba)_3$ which both gave lower yields and enantioselectivities of the cyclized product (Table 1, entries 8–9).

Table 3. Asymmetric Pd-Catalyzed Intramolecular Arylation of α-Ketimino Amides **1**–**9**[a]



entry	product		yield[b] (%)	ee[c] (%)
1		**1a**	95	84 (-)
2		**2a**	76	88 (-)
3[d]		**3a**	58	82 (-)
4[d]		**4a**	91	51 (-)
5[d]		**5a**	87	84 (-)
6[d]		**6a**	87	96 (+)
7[d]		**7a**	47	86 (-)
8[d]		**8a**	81	88 (-)
9[d]		**9a**	83	80 (92) (-)

[a] Reaction conditions: 0.1 mmol of substrate, 5 mol % $[Pd(CH_3CN)_4](BF_4)_2$, 10 mol % (*R*)-DiFluorPhos, 0.25 mmol of Et_3N, 0.8 mL of toluene, 100 °C, 16–24 h. [b] Isolated yield after purification by flash chromatography. [c] Determined by chiral HPLC. An average *ee* after two runs. Absolute configuration of **1a** was determined (see Supporting Information), and thereafter absolute configurations were assigned to (*S*) by analogy. [d] 10 mol % $[Pd(CH_3CN)_4](BF_4)_2$ and 20 mol % (*R*)-DiFluorPhos were used.

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(23) See Supporting Information for full details.

We also decided to investigate the effect of catalyst loading and the Pd/ligand ratio on the enantioselectivity and efficiency of the reaction (Table 1, entries 1−4). It can be seen clearly that 5 mol % of palladium was required for the reaction to proceed in an efficient and enantioselective matter. Additionally, when the Pd/ligand ratio was 1:2, a higher enantioselectivity was obtained. Optimization of the reaction conditions showed that the use of toluene and trifluoromethylbenzene gave higher enantioselectivities than the more polar solvents acetonitrile and 1,4-dioxane (Table 1, entries 1 and 5−7). Interestingly, these reaction conditions were also optimal for the intramolecular arylation of α-keto amides as found in a seminal work by Shibasaki.[15]

We wanted to explore further if substrates other than aryl triflates could be employed in this transformation, and therefore we investigated the use of an aryl iodide in the intramolecular arylation of **2** (Table 2). This change had a strong effect on overall conversion and an even more dramatic effect on the enantioselectivity of the reaction. Under the usual reaction conditions using $[Pd(CH_3CN)_4](BF_4)_2$ with the aryl iodide, only a trace of the desired product was observed (Table 2, entries 1 and 2). The reaction was then investigated with $Pd(P(o\text{-}Tol)_3)_2$ as an alternative source of palladium (Table 2, entries 3−5). The asymmetric arylation of aryl triflate employing this precursor resulted in high enantioselectivity, but only partial conversion of the reactant was observed. In contrast to the aryl triflate, the corresponding aryl iodide only delivered the racemic product in low yield (Table 2, entries 3 and 4). When a stoichiometric amount of AgOTf was added to the reaction mixture, almost complete conversion was obtained (Table 2, entry 5). However, the enantioselectivity remained lower as compared with aryl triflates.

After the initial reaction optimization we evaluated the substrate scope of the reaction (Table 3). The asymmetric Pd-catalyzed intramolecular arylation of subtrates with varying R^1-substituents ranging from alkyl to aryl gave good to excellent yields and enantioselectivities up to 88% *ee* (Table 3, entries 1−3). When R^1 was a heteroaromatic substituent such as indole, no cyclized product was observed. We also investigated the imine substituent (R^2) tolerance (Table 3, entries 4−6). This substituent had a large influence on the conversion of the reaction. With both electron-withdrawing (R^2 = *p*-Cl-C_6H_4) and electron-donating (R^2 = *p*-Me-C_6H_4, *p*-OMe-C_6H_4) substituents attached to the aromatic ring, the reaction proceeded to full conversions when the catalyst loading was increased to 10 mol %. The enantioselectivities varied significantly, with the lowest observed enantioselectivity arising when an electron-donating OMe-substituent (51% *ee*) is present and the highest observed enantioselectivity with an electron-withdrawing Cl-substituent (96% *ee*). The α-ketimino amides possessing R^1 = Me (**2**, **7**, and **8**) all gave enantioselectivities within the range 84−88% *ee* (Table 3, entries 2, 7, and 8).[24] To provide a further possibility for functionalization via cross-coupling techniques, we also included a chloride-substituted oxindole core structure in our substrate scope studies (Table 3, entry 9). This reaction gave the desired 3-amino-2-oxindole (together with a minor amount of inseparable impurity) with consistent enantioselectivity for the cyclized product as compared with the previous results (80% *ee*). After a single recrystallization the enantiopurity of this product was enhanced to 92% *ee*.

In conclusion we have demonstrated a new synthetic route to enantiomerically enriched 3-amino-2-oxindoles by palladium catalysis. Also this report represents the first example of an asymmetric palladium-catalyzed arylation of imines, which we believe is an area of future interest in catalysis. Investigation on the reaction mechanism and the origin of enantioselectivity is underway in our laboratory.

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Supporting Information Available. Experimental procedures for the substrates and products, compound characterization, spectra, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

(24) Alkyl substiuent as the R^2-substituent gave only a trace of desired 3-amino-2-oxindole product under the standard reaction conditions.

The authors declare no competing financial interest.