Asymmetric Catalysis

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A Facile Pathway to Enantiomerically Enriched 3-Hydroxy-2-Oxindoles: Asymmetric Intramolecular Arylation of α-Keto Amides Catalyzed by a Palladium–DifluorPhos Complex**

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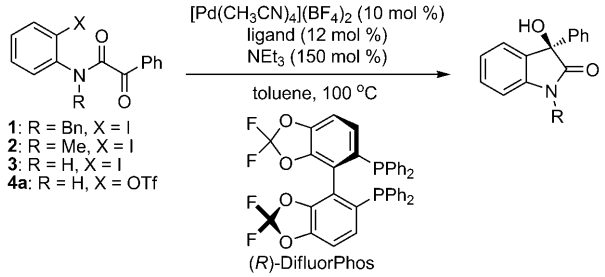
Organic group-transfer reactions from halides and triflates to carbonyl compounds are a useful C–C bond-forming transformation. An example is the chromium-mediated Nozaki–Hiyama–Kishi (NHK) reaction,[1] whose utility has been demonstrated by numerous applications to total syntheses of complex natural products and biologically active compounds.[2] The requirement for stoichiometric amounts of toxic chromium salts—a major drawback of this reaction—has been overcome by the use of a catalytic redox system developed by Fürstner and Shi.[3] This fundamental achievement allowed for extension to a catalytic enantioselective variant of the NHK reaction.[4] Despite the great advantages of the catalytic system compared to the original stoichiometric system, the requirements for stoichiometric amounts of Mn^0 and TMSCl still conflicts with principles of modern, environmentally benign synthetic organic chemistry.[5] A catalytic asymmetric NHK-type (or Grignard/Barbier-type) reaction without the use of stoichiometric amounts of metals is therefore in high demand.

In 2000, Yamamoto and co-workers reported a unique racemic reaction that would potentially satisfy the above demand; a palladium-catalyzed intramolecular aryl-transfer reaction from aryl iodides and bromides to ketones using a primary alcohol as the stoichiometric reductant.[6] A catalytic asymmetric variant of this synthetically useful reaction, with minimal use of metals, has yet to be developed. Combined with our ongoing interest in the catalytic asymmetric synthesis of 3-hydroxy-2-oxindoles with an arylic tetrasubstituted carbon center,[7–12] we began a project to develop a catalytic enantioselective intramolecular arylation reaction of α-keto anilides by modifying Yamamoto's original protocol.[13] The products of this reaction are versatile chiral synthetic intermediates for biologically active compounds.[14] Herein, we report the first example of such a reaction.

We began our study by examining the reaction using α-keto 2-iodoanilide **1** as a substrate in the presence of (*R*)-tol-binap complex of Pd^0 as the catalyst (10 mol%) and Et_3N as a reductant (Table 1). Our initial screening of [Pd] sources

Table 1: Optimization of reaction conditions.



Entry	Substrate	Ligand	*t* [h]	Yield [%][a]	*ee* [%][b]
1[c]	**1**	(*R*)-tol-binap	12	15	8
2[d]	**1**	(*R*)-tol-binap	12	93	33
3[d]	**2**	(*R*)-tol-binap	12	61	34
4[d]	**3**	(*R*)-tol-binap	12	68	78
5[d]	**3**	(*R*)-DifluorPhos	12	47	91
6[d]	**4a**	(*R*)-DifluorPhos	12	25	89
7[e,f]	**4a**	(*R*)-DifluorPhos	24	87	91
8[e,g]	**4a**	(*R*)-DifluorPhos	48	75	91
9[e,h]	**4a**	(*R*)-DifluorPhos	120	68	87

[a] Yield of isolated product. [b] Determined by HPLC on a chiral stationary phase. [c] 1.5 equivalents of Na_2CO_3 added. [d] 1.5 equivalents of Ag_3PO_4 added. [e] In the presence of 2.5 equivalents of Et_3N. [f] 5 mol% of [Pd] and 6 mol% of ligand used. [g] 2.5 mol% of [Pd] and 3 mol% of ligand used. [h] 1.25 mol% of [Pd] and 1.5 mol% of ligand used. Bn = benzyl, Tf = trifluoromethanesulfonyl.

indicated that $[Pd(CH_3CN)_4](BF_4)_2$ was optimal, although the yield and enantioselectivity were low (Table 1, entry 1). Based on previous findings in Heck chemistry indicating that 16-electron species are favored over 18-electron complexes of Pd, we decided to examine the effects of silver salt additives to generate a cationic 16-electron pretransition-state intermediate (see **11** in Scheme 3).[15] The addition of 1.5 equivalents of Ag_3PO_4 improved both yield and enantioselectivity, and the product was obtained with 33% *ee* (Table 1, entry 2). *N*-Methyl-substituted substrate **2** afforded comparable enantioselectivity (Table 1, entry 3). On the other hand, enantioselectivity was markedly improved using substrate **3** without a protecting group on the nitrogen atom

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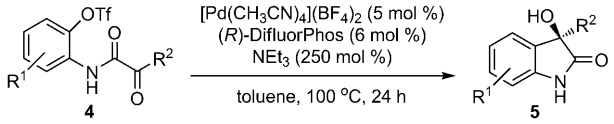
(78% ee; Table 1, entry 4). Different types of chiral phosphines were examined at this stage, and (*R*)-DifluorPhos[16] was identified as the best ligand in terms of enantioselectivity (Table 1, entry 5).[17] To increase the reactivity, aryl triflate **4a** was used as a substrate instead of the iodide. Unfortunately, product **5a** was obtained in only 25% yield (Table 1, entry 6). Removal of Ag_3PO_4 and increasing the amount of Et_3N to 2.5 equivalents, however, afforded **5a** in excellent yield and high enantioselectivity was maintained (Table 1, entry 7). The reaction was performed in the presence of 2.5 mol% of [Pd] and 3 mol% of ligand and afforded the product in slightly decreased yield and with consistent enantioselectivity (Table 1, entry 8). Furthermore, catalyst loading could be decreased to 1.25 mol% to afford a synthetically useful yield and enantioselectivity, although the reaction time was longer (Table 1, entry 9).

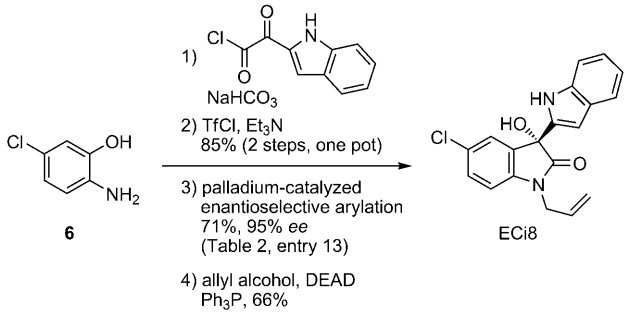
Next, the substrate scope was investigated under the optimized conditions using 5 mol% catalyst (Table 2). Both electron-donating and electron-withdrawing substituents were tolerated on both of the aromatic rings at the aniline and ketone sides of the molecule (Table 2, entries 1–11). The aryl triflate moiety was selectively activated in the presence of an aryl chloride moiety (Table 2, entry 5), and oxindole **5e** was produced in a synthetically useful yield (63%) with excellent enantioselectivity (93% *ee*). Substrates with a heteroaromatic substituent at the ketone also afforded excellent results (Table 2, entries 12 and 13). Specifically, substrate **4m** with a non-protected indole and an aryl chloride moieties produced **5m** with 95% *ee* (Table 2, entry 13). This reaction was performed in a gram scale and was a key step in the catalytic enantioselective synthesis of ECi8, which is a potent antimicrobial lead drug.[18] The synthesis was completed in four steps from commercially available aminophenol **6** (40% overall yield; Scheme 1).[17] The reaction was also applicable to aliphatic α-keto anilides, and afforded the corresponding products in high enantioselectivity (Table 2, entries 14–18). Despite the existence of several catalytic enantioselective methods for the synthesis of 3-aryl- and 3-alkenyl-3-hydroxy-2-oxindoles,[7,9b–f,11,12b] the catalytic enantioselective oxidation of indolinones[12a] is the only reported method generally applicable to the synthesis of the related compounds substituted with a simple alkane at the 3-position. Synthesis of the substrates for the catalytic enantioselective oxidation, however, was not necessarily straightforward.[12a] Therefore, the current method is noteworthy with regard to the broad substrate scope, the overall practicality which includes chemical stability (compared to organometallic reagents), and the easy accessibility[17] of substrates **4**.

Table 2: Catalytic enantioselective intramolecular arylation of α-keto amides to generate 3-hydroxy-2-oxindoles.



Entry	Product	Yield [%][a]	*ee* [%][b]
1	**5a**: $R^1 = H$	87	91[c]
2	**5b**: $R^1 = 5\text{-}CH_3$	83	87
3	**5c**: $R^1 = 6\text{-}CH_3$	92	90
4	**5d**: $R^1 = 7\text{-}CH_3$	88	89
5	**5e**: $R^1 = 6\text{-}Cl$	63	93
6	**5f**: $R^1 = 6\text{-}CH_3O$	87	82
7	**5g**	83	84
8	**5h**: $R^3 = 2'\text{-}CH_3$	93	90
9[d]	**5i**: $R^3 = 2'\text{-}CH_3O$	92	89
10[d]	**5j**: $R^3 = 4'\text{-}CH_3O$	87	89
11	**5k**: $R^3 = 4'\text{-}F$	85	99
12	**5l**	86	90
13[e]	**5m**	71	95
14	**5n**: $R^2 = CH_3$	55	88[c]
15	**5o**: $R^2 = CH_3CH_2$	53	88
16	**5p**: $R^2 = (CH_3)_2CH$	74	83
17	**5q**: $R^2 = (CH_3)_2CHCH_2$	82	84
18	**5r**: $R^2 = (E)\text{-}PhCH{=}CH$	55	89

[a] Yield of isolated product. [b] Determined by HPLC on a chiral stationary phase. [c] Absolute configuration was assigned to be *R*[17]. For other entries, the absolute configuration was temporarily assigned based on analogy to **5a** and **5n**. [d] Reaction time was 30 h. [e] (*S*)-DifluorPhos used.



Scheme 1. Four-step catalytic enantioselective synthesis of ECi8.

Furthermore, the current method is potentially applicable to the catalytic enantioselective synthesis of 4-hydroxydihydroquinolinone derivatives **8** (Scheme 2). Despite their high synthetic utility as chiral building blocks for drug candidates,[19] there has been no straightforward catalytic asymmetric route to such compounds. Although enantioselectivity is still moderate at this stage, a highly hindered tetrasubstituted carbon center was constructed in a synthetically useful yield with good enantioselectivity.[17]

Finally, a possible catalytic cycle and enantio-differentiation models are proposed in Scheme 3, partly based on previous reports.[6,20] First, $[Pd(CH_3CN)_4](BF_4)_2$ is reduced by Et_3N in the presence of (*R*)-DifluorPhos to afford **9**. Subsequently, **9** reacts with the aryl triflate substrate to afford aryl palladium complex **10**, which has six-membered

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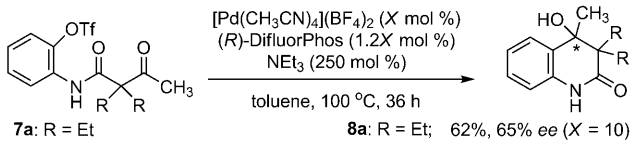
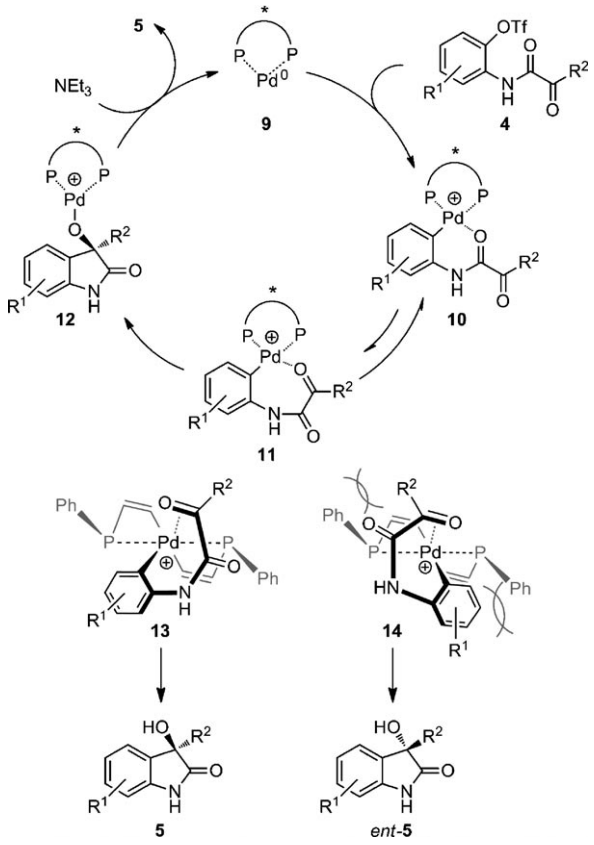


Scheme 2. Catalytic enantioselective intramolecular arylation of β-keto amides to generate 4-hydroxydihydroquinolin-2-one. DEAD = diethyl azodicarboxylate.



Scheme 3. Postulated catalytic cycle and enantio-differentiation models. The structure of DifluorPhos is simplified in **13** and **14** to illustrate the relevant moieties for the enantio-differentiation.

coordination of the amide carbonyl oxygen atom.[20,21] This kinetically and thermodynamically favorable species **10** would exist under equilibrium with **11**, which has seven-membered coordination. Insertion of the ketone carbonyl group into the aryl palladium bond would proceed from **11**, thus producing enantiomerically enriched palladium alkoxide species **12**, which is reduced by the amine to regenerate catalytically active **9** with liberation of product **5**. The enantio-differentiating insertion should proceed through **13**, thereby exhibiting less steric congestion than **14**, to produce the enantiomer of product **5**.

In summary, we developed the first palladium-catalyzed enantioselective intramolecular aryl-transfer reaction of aryl triflates to ketones. Triethylamine was utilized as a stoichiometric reductant and a base, thus eliminating the use of stoichiometric amounts of metals. Further studies toward improvement of the 4-hydroxydihydroquinolinone synthesis as well as expansion of the substrate scope are ongoing.

Experimental Section

General procedure: Complex $[Pd(CH_3CN)_4](BF_4)_2$ (8.9 mg, 0.02 mmol), (*R*)-DifluorPhos (16.4 mg, 0.024 mmol), and dry toluene (1.0 mL) were added to a flame-dried flask under argon. The solution was stirred for 5 min, before dry Et_3N (145 μL, 1.0 mmol) and a solution of aryl triflate **4** (1.0 mL, 0.4 mmol) in toluene were added. The reaction mixture was then heated at 100 °C. After completion of reaction (as evident by TLC), the mixture was purified by column chromatography on silica gel (eluent: hexanes/AcOEt = 3/1→1/1) to afford pure 3-hydroxy-oxindole **5**.

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[21] Studies of the substrate scope and limitations supported the importance of the six-membered coordination of the amide oxygen atom to the palladium after oxidative addition. See the Supporting Information for details.

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