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## Nickel-Catalyzed Intramolecular Nucleophilic Addition of Aryl or Vinyl Chlorides to α-Ketoamides Through C–Cl Bond Activation

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Organopalladium and organonickel intermediates derived from aryl or vinyl halides through oxidative addition to Pd<sup>0</sup> and Ni<sup>0</sup> complexes predominantly act as electrophiles in carbon-carbon bond-forming reactions.<sup>[1]</sup> In contrast, their nucleophilic reactivity has received much less attention; however, the development of the direct catalytic nucleophilic reaction of aryl or vinyl halides with electrophilic partners is very attractive because it omits the preparation of active nucleophilic organometallic reagents.<sup>[2]</sup> Recently, there have been a few literature examples reported for this direct nucleophilic addition to carbon-heteroatom bonds under relatively forcing reaction conditions; however, most of the substrates were more reactive aryl bromides and iodides.<sup>[3]</sup> Despite their wide diversity, availability, and low cost, aryl chlorides have rarely been studied in this area probably due to their low reactivity,<sup>[4,5]</sup> which has often been ascribed to their higher bond energy and makes activation by a homogenous transition-metal catalyst more difficult (bond dissociation energies (kcalmol<sup>-1</sup>) for Ph-X: Cl (95); Br (80); I (65)).<sup>[6]</sup> In the last decade, owing to the introduction of electron-rich bulky phosphine or carbene ligands, great advance has been made for the utilization of aryl chlorides as electrophilic partners in the cross-coupling reaction. These bulky ligands are thought to facilitate the oxidative addition of the C-Cl bond of the aryl chloride to the metal catalyst, which is the initial crucial step required to activate the C-Cl bond in this type of transformation.<sup>[7]</sup> Enlightened by these results, we envisioned that the nucleophilic addition reaction of aryl chlorides might be realized by introducing the appropriate above-mentioned ligand, because it facilitates the same initial oxidative addition reaction and its ligation to

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the organo-transition-metal intermediates may improve their nucleophilicity.<sup>[5]</sup> Herein, we present the primary results of a nickel-catalyzed intramolecular addition of aryl or vinyl chlorides<sup>[8]</sup> to ketoamides, through C–Cl bond activation under mild conditions (Scheme 1).



Scheme 1. Nickel-catalyzed intramolecular addition of aryl or vinyl chlorides to ketoamides.  $PCy_3 = tricyclohexylphosphine$ .

To find a potential metal catalyst, we initially studied the intramolecular reaction of the chloro substrate 1a in the presence of a stoichiometric amount of metal/tricyclohexyl-phosphine (PCy<sub>3</sub>) complex (Scheme 2) Fortunately, [Ni-



Scheme 2. [Ni(cod)<sub>2</sub>]/PCy<sub>3</sub> promoted intramolecular reaction of 1a

 $(cod)_2$  (cod = 1,5-cyclooctadiene) was found to promote the reaction of 1a at 70°C in 4 h to give 2a, isolated in 89% yield (Scheme 2), whereas no conversions were observed when  $[Pd(dba)_2]$  (dba = dibenzylideneacetone) and CuI were used to promote the reaction. We then focused on the development of the catalytic version with a nickel catalyst. To our delight, although Et<sub>3</sub>B and zinc dust were inefficient (Table 1, entries 11 and 12), Me<sub>2</sub>Zn accelerated the catalytic reaction (when used in combination with  $[Ni(cod)_2]$ (5 mol %) and PCy<sub>3</sub> (10 mol %)) to give oxindole **2a** in 89% yield (as calculated from <sup>1</sup>H NMR data, Table 1, entry 1). Et<sub>2</sub>Zn was found to be less efficient than Me<sub>2</sub>Zn (Table 1, entry 9 vs. entry 10). Among the monodentate ligands tested, PCy3 was found to be the most efficient (Table 1, entries 1-3), but the yields were markedly lower when using the bidentate ligand diphenylphosphine ethane (dppe) or without using any ligand (Table 1, entries 4 and 5). A screen of the reaction solvent revealed that dimethoxyethane (DME) was the best, which enabled 2a to be isolated in Table 1. Optimization of the nickel-catalyzed reaction.<sup>[a]</sup>

		Ph Ni cat. (5 mol%) L (10 mol%) reductant (2.0 equiv) solvent, 40°C, 12h		HO Ph N		
1a				2a		
Entry	Ni cat.	Ligand (L)	Reductant <sup>[b]</sup>	Solvent	Yield [%] <sup>[c]</sup>	
1	[Ni(cod) <sub>2</sub> ]	PCy <sub>3</sub>	Me <sub>2</sub> Zn	THF	89	
2	$[Ni(cod)_2]$	PPh <sub>3</sub>	$Me_2Zn$	THF	82	
3	$[Ni(cod)_2]$	PtBu <sub>3</sub> •HBF <sub>4</sub>	$Me_2Zn$	THF	72	
4	$[Ni(cod)_2]$	dppe	$Me_2Zn$	THF	33	
5	$[Ni(cod)_2]$	_	$Me_2Zn$	THF	21	
6	$[Ni(cod)_2]$	PCy <sub>3</sub>	$Me_2Zn$	Toluene	60	
7	$[Ni(cod)_2]$	PCy <sub>3</sub>	$Me_2Zn$	Ether	21	
8	$[Ni(cod)_2]$	PCy <sub>3</sub>	$Me_2Zn$	$CH_2Cl_2$	0	
9	$[Ni(cod)_2]$	PCy <sub>3</sub>	$Me_2Zn$	DME	98 (95) <sup>[d]</sup>	
10	$[Ni(cod)_2]$	PCy <sub>3</sub>	$Et_2Zn$	DME	80 <sup>[d]</sup>	
11	[Ni(cod) <sub>2</sub> ]	PCy <sub>3</sub>	Et <sub>3</sub> B	DME	0	
12	$[Ni(cod)_2]$	PCy <sub>3</sub>	Zn dust	DME	0	
13	[Ni(acac) <sub>2</sub> ]	PCy <sub>3</sub>	$Me_2Zn$	DME	93	
14	[NiCl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub> ]	-	$Me_2Zn$	DME	88	
15	_	PCy <sub>3</sub>	$Me_2Zn$	DME	0	

[a] Reaction conditions: **1a** (0.2 mmol) in solvent (2 mL) at 40 °C. cod = 1,5-cyclooctadiene; acac=acetylacetonate;  $PCy_3$ =tricyclohexylphosphine; dppe=diphenylphosphine ethane; DME=1,2-dimethoxyethane. [b] Me<sub>2</sub>Zn (2.0 m in toluene); Et<sub>2</sub>Zn (1.0 m in hexane); Et<sub>3</sub>B, (2.0 m in hexane). [c] Yield calculated from <sup>1</sup>H NMR analysis, using 1-methoxy-2,3-dimethylbenzene as the internal standard. [d] Yield of isolated product.

95% yield (Table 1, entry 9). Finally, an investigation of the catalyst precursor disclosed that  $[Ni(acac)_2]$  (acac=acetyl-acetonate) was nearly as efficient as  $[Ni(cod)_2]$  (Table 1, entry 13), however the preformed catalyst  $[NiCl_2(PCy_3)_2]$  slightly decreased the yield (Table 1, entry 14). Not surprisingly, the reaction could not proceed without a nickel catalyst (Table 1, entry 15).

We next investigated the substrate scope; a series of chloro substrates were tested under the optimal reaction conditions established above (Table 1, entry 9). As shown in Scheme 3, all the reactions afforded the corresponding 3-hy-



Scheme 3. Substrate scope of the intramolecular addition reaction with aryl or vinyl chlorides. For 2a-2n, reaction conditions are identical to Table 1, entry 9. The reaction time was 12h (except 2n, in which the reaction time was 18h). For 2o-2r, [NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub>] (5 mol %) was used as the catalyst in 1,4-dioxane at 50 °C for 10h. Napthth = naphthalene

droxyoxindoles (2a-2n) in good to excellent yields, except oxindole 21 (with an alkyl group (phenylethyl) at the 3-position), which was obtained in a lower yield. In addition, high chemoselectivities were observed and no methylation byproducts from the cross-coupling of aryl chloride with Me<sub>2</sub>Zn were detected. It is noteworthy that excellent yields were attained for the synthesis of oxindoles 2h and 2m, in which the chlorides remained unreacted and ready for further functionalization. As shown in Scheme 4, the biaryl



Scheme 4. Suzuki coupling of 2h and 2m with PhB(OH)2.

products were obtained in excellent yields by a Pd-catalyzed Suzuki-coupling of **2h** and **2m** with PhB(OH)<sub>2</sub>. Although the cross-coupled methylation byproduct was observed (<10% yield), this process was further extended to the analogous vinyl chlorides and the intramolecular reaction proceeded well with [NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub>] (5 mol%) as the catalyst in 1,4-dioxane at 50°C, to give the corresponding pyrrolidinones **2o-2r** in moderate to good yields (Scheme 3).

The scope of bromo substrates was also probed under the same reaction conditions. As expected and shown in Scheme 5, the reactivity of aryl bromides was generally higher than that of the analogous chlorides, giving the oxindoles in excellent yields. For the synthesis of pyrrolidinones, the reactions could be carried out at room temperature and good yields were observed except for the product 2u. Notably, the product 2q was obtained in high yield and the chloride was retained as in the case of 2h and 2m. The adduct 5 was formed instead of the desired oxindole for the reaction of 4, indicating that the presence of a free N–H bond in the substrate was incompatible with this transformation.



Considering the mechanism, the following pertinent results are worth noting: 1) The stoichiometric reaction of **1a** and the  $[Ni(cod)_2]$  complex of PCy<sub>3</sub> revealed the nucleophilicity of the aryl–nickel intermediate, derived from the oxidative addition of aryl chloride to Ni<sup>0</sup>, which is similar to the Grignard reagent (Scheme 2); 2) The reaction of aryl bromide **6** with dimethylzinc was examined under the reac-

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Scheme 5. Substrate scope of the intramolecular addition reaction with aryl or vinyl bromides. The reaction conditions for oxindole synthesis are identical to entry 9 of Table 1. For pyrrolidinone synthesis,  $[NiCl_2(PCy_3)_2]$  (5 mol%) was used as the catalyst in 1,4-dioxane at 25 °C for 6 h.

tion conditions; only a 6% yield of **7** obtained from the cross-coupling of **6** with Me<sub>2</sub>Zn was isolated in 4 h (25% in 14 h) incorporating a trace amount of dehalogenated product, which was consistent with the observation by Subburaj and Montgomery.<sup>[9]</sup> This excludes the involvement of the nucleophilic aryl–zinc species in the addition step thus implying the role of Me<sub>2</sub>Zn as reducing agent and base in the reaction (Scheme 6); 3) Low but important enantiomeric



Scheme 6. Conversion of **6** under the established reaction conditions.

excess (*ee*) values were detected when the chiral phosphoramidite ligand (8, (R,S,S)-MonoPhos-PE) was introduced into the reaction of **1a** or **3a** (Scheme 7), which further sup-



Scheme 7. Asymmetric reaction.

ported the theory that the aryl–nickel intermediate was most likely involved in the nucleophilic addition step and hence asymmetric induction was observed. On the basis of the above observations, we proposed the reaction pathway shown in Scheme 8. The nucleophilic addition occurs after the generation of the nucleophilic aryl–nickel intermediate A through oxidative addition to give the adduct B, followed by metathesis with  $Me_2Zn$ , to afford the product precursor D and the Ni<sup>II</sup> species C, which is reduced to Ni<sup>0</sup> in the presence of  $Me_2Zn$  to fulfill the catalytic cycle (Scheme 8). In summary, for the first time we have developed an efficient process for the direct nucleophilic addition of aryl and vinyl chlorides to ketoamides for the construction of 3-hydroxyoxindoles and pyrrolidinones under mild reaction conditions. This method was then successfully extended to the analogous bromides. Further application of this method to other electrophilic substrates, the develop-



Scheme 8. Proposed mechanism for the nucleophilic addition reaction.

ment of an asymmetric version, and the detailed mechanistic study are in progress in our laboratory.

## **Experimental Section**

**Synthesis of 2a:**  $[Ni(cod)_2]$  (2.8 mg, 0.01 mmol) and PCy<sub>3</sub> (5.7 mg, 0.02 mmol) was added to a dried Schlenk tube under N<sub>2</sub>, and then freshly distilled DME (2 mL) was introduced by a syringe. The resulting mixture was stirred at room temperature for 1 h before addition of the substrate **1a** (56 mg, 0.2 mmol) under N<sub>2</sub>, followed by treatment with a solution of Me<sub>2</sub>Zn in toluene (0.2 mL, 2M). The reaction mixture was then stirred at 40 °C for 12 h (reaction monitored by TLC). After cooling to room temperature, the mixture was quenched with sat. NH<sub>4</sub>Cl (5 mL). Extraction with diethyl ether (2×10 mL), drying of the combined organic phases over MgSO<sub>4</sub>, and final evaporation of the ether afforded a crude product that was then purified by flash chromatography to give oxindole **2a** (46.5 mg, 95%).

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## COMMUNICATION

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