



Nickel-catalyzed intramolecular addition of vinyl or aryl bromides to ketoamides



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ABSTRACT

A nickel-catalyzed intramolecular addition of vinyl or aryl bromides to ketoamides has been developed. The reactions proceeded efficiently with $\text{Ni}(\text{bpy})\text{Br}_2$ as a catalyst and zinc powder as reducing agent, affording 3-hydroxypyrrolidinones, 3-hydroxyoxindoles, and dihydroquinolinones as important heterocyclic compounds in good to excellent yields.

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The addition of aryl or vinyl fragments to carbonyl compounds is an important synthetic access to benzylic or allylic alcohols. Conventional methods rely on the nucleophilic addition of active organometallic reagents to $\text{C}=\text{O}$ bonds, whereas the nucleophilic

organometallic reagents are normally prepared from aryl or vinyl halides and are incompatible with sensitive functional groups in most cases.¹ Undoubtedly, elegant method would be the direct addition of aryl or vinyl halides to $\text{C}=\text{O}$ bonds. In this context,

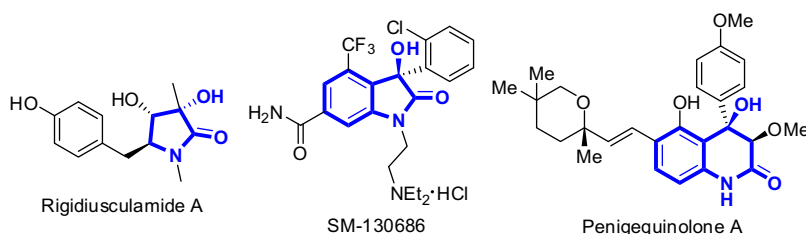
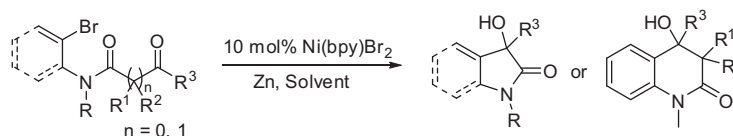


Figure 1. Selected molecules containing 3-hydroxypyrrolidinone, 3-hydroxyoxindole, and dihydroquinolinone structural motifs.



Scheme 1. Nickel-catalyzed addition of vinyl or aryl bromides to ketoamide.

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the Nozaki–Hiyama–Kishi (NHK) reaction, addition of organohalides to aldehydes via generation of nucleophilic organochromium species in situ, offers an attractive strategy to alcohols, while the

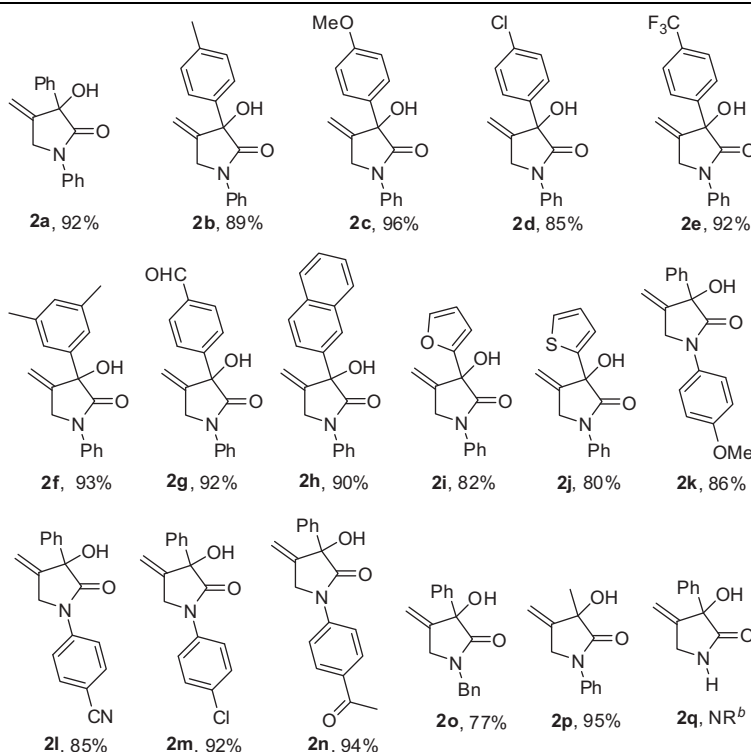
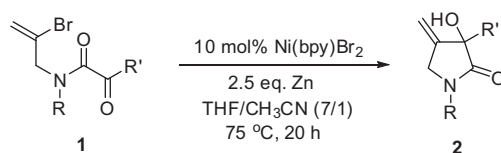
Table 1
Optimization of the reaction of **1a**^a

Entry	[Ni]	Solvent	Time (h)	Yield ^b (%)
1	Ni(dppe)Br ₂	THF	72	88
2	Ni(dppe)Br ₂	1,4-Dioxane	72	34
3	Ni(dppe)Br ₂	DMF	72	66
4	Ni(dppe)Br ₂	Toluene	36	Trace
5	Ni(dppe)Br ₂	CH ₃ CN	36	Trace
6	Ni(dppe)Br ₂	THF/CH ₃ CN (3/1)	36	70
7	Ni(dppe)Br ₂	THF/CH ₃ CN (7/1)	36	89
8	Ni(dppe)Br ₂	THF/CH ₃ CN (19/1)	72	88
9	Ni(dppp)Br ₂	THF/CH ₃ CN (7/1)	36	90
10	Ni(PCy ₃) ₂ Br ₂	THF/CH ₃ CN (7/1)	36	59
11	Ni(bpy)Br ₂	THF/CH ₃ CN (7/1)	20	92

^a Reactions conditions: 0.2 mmol **1a**, 10 mol % catalyst, and 2.5 equiv Zn in 4.0 mL solvent at 75 °C. dppe = 1,2-bis(diphenylphosphino)ethane; PCy₃ = tricyclohexylphosphine; dppp = 1,3-bis(diphenylphosphino)propane; bpy = 2,2'-bipyridine.

^b Isolated yield.

Table 2
Substrate scope for the reaction of vinyl bromides **1**^a



^a Reactions conditions: 0.2 mmol of the substrate **1**, 10 mol % Ni(bpy)Br₂, 2.5 equiv Zn in 4.0 mL THF/CH₃CN (7/1) at 75 °C for 20 h; Isolated yield.

^b No reaction.

substrate was limited to aldehydes.² Recently, the Pd-catalyzed addition of aryl halides to a range of carbon-heteroatom multi-bonds has been intensely developed by using the rare nucleophilic property of organopalladium species.^{3–5} Nickel complexes also showed unique catalytic activities in these transformations, thus, the reactions of aryl halides to aldehydes,⁶ isocyanates,⁷ and *N,N*-dimethylformamide⁸ were efficiently catalyzed by nickel complex. Nevertheless, the utilization of ketone as substrate in this field remains less exploited. And, the reaction of vinyl halides and carbon-heteroatom multi-bonds was fairly rare in spite that the additions of in situ generated vinylpalladium or vinylnickel species to carbon-heteroatom multi-bonds have been extensively involved in the annulations of *ortho*-halo aryl aldehydes,⁹ ketones,¹⁰ or nitriles¹¹ with alkynes.

We have previously documented a Ni(COD)₂/PCy₃ catalyzed intramolecular addition of aryl chlorides or bromides to α -ketoamides, furnishing oxindoles in excellent yields with Me₂Zn as reducing agent.¹² However, the reaction of vinyl halides was not successful due to the undesired Negishi-coupling reaction between vinyl halides and Me₂Zn, which resulted in modest yields of the products. We disclosed herein a NiBr₂/bipyridine complex catalyzed intramolecular reaction of vinyl or aryl bromides and keto-amides, affording 3-hydroxypyrrolidinones, 3-hydroxyoxindoles, and dihydroquinolinones, important substructural motifs existed in natural products and biologically active molecules (Fig. 1),¹³ in good to excellent yields in the presence of zinc powder as reducing

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