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COMMUNICATION

Ni-Catalyzed α -Arylation of Esters and Amides with Phenol Derivatives

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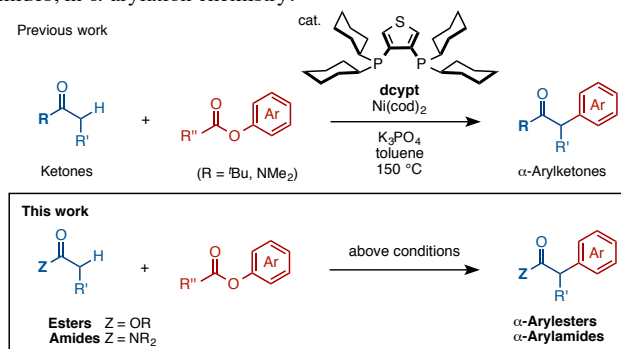
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A nickel-catalyzed α -arylation of esters and amides with phenol derivatives has been accomplished. In the presence of our unique nickel catalyst, prepared in situ from Ni(cod)₂ and 3,4-bis(dicyclohexylphosphino)thiophene (dcypt), and K₃PO₄, various esters and amides undergo α -arylation with *O*-arylpivalates or *O*-arylcabamates to afford the corresponding coupling products. The thus-obtained α -aryl esters and amides are useful precursors of privileged motifs such as α -arylcarboxylic acids and β -arylamines.

α -Aryl esters and amides are useful intermediates in organic synthesis that can be converted into prevalent motifs such as α -arylcarboxylic acids and β -arylamines.¹ Therefore, over the last two decades, significant efforts have been devoted to develop concise, direct, and environmentally friendly methods constructing these privileged motifs. A representative method for the synthesis of α -aryl esters and amides is the Pd-catalyzed α -arylation of esters and amides with (pseudo)haloarenes. A number of reaction conditions have been reported by several groups including Miura, Hartwig and Buchwald, who are the pioneers in this field.^{2,3} However, these state-of-the-art α -arylation reactions typically necessitate expensive Pd catalysts as well as haloarenes as arylating agents.^{4,5} Herein, we report that our unique nickel catalyst allows the α -arylation of esters and amides with phenol derivatives as arylating agents and K₃PO₄ as a mild base.

In recent years, phenol derivatives have received much attention as green and inexpensive arylating agents via C–O activation (alternative to haloarenes) in coupling chemistry.^{6,7} Our group has also contributed to this field by developing unique nickel catalysts that can activate not only the phenolic C–O bonds but also the C–H bonds of counter coupling components to achieve otherwise difficult C–H/C–O activation/coupling processes. For example, in the presence of a nickel catalyst prepared from Ni(cod)₂ (cod = 1,5-cyclohexadiene) and 1,2-bis(dicyclohexylphosphino)ethane (dcype), the C–H/C–O type coupling of 1,3-azoles and phenol derivatives can be realized.⁸

Very recently, we translated the established nickel-based C–H/C–O activation mode to α -arylation of ketones with phenol derivatives (*O*-arylpivalates or *O*-arylcabamates), which addresses some of the drawbacks in the state-of-the-art α -arylation chemistry (Scheme 1).⁹ During this study, we found that the newly developed ligand, 3,4-bis(dicyclohexylphosphino)thiophene (dcypt), is superior to our first-generation ligand dcype. Encouraged by the facts that our new ligand not only displays high reactivity in activating C–H and C–O bonds but is also stable in air, we wondered whether the Ni(cod)₂/dcypt catalyst can be applied to a more challenging class of substrates, esters and amides, in α -arylation chemistry.

Scheme 1 Ni-catalyzed α -arylation of carbonyl compounds

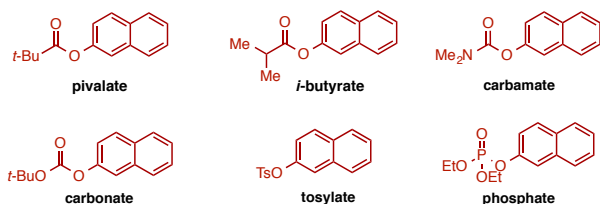
We began by investigating the coupling reaction of representative carbonyl compounds (ketone **1A**, ester **1B**, and amide **1C**) and phenol derivatives (Ar–OR) in the presence of Ni(cod)₂/dcypt catalyst (Table 1). In order to study the trend in reactivity, carbonyl compounds (**1A**–**1C**; 1.5 equiv) were treated with Ar–OR (**2**; 1.0 equiv) in toluene at 150 °C for 24 h, in the presence of Ni(cod)₂ (10 mol%), dcypt (20 mol%), and K₃PO₄ (1.5 equiv). Ketone **1A** was coupled with naphthalen-2-yl pivalate (“pivalate”) and naphthalen-2-yl dimethylcarbamate (“carbamate”) to afford the corresponding product **3A** in 91% and 77% isolated yields, respectively (Entries 1 and 2).⁹

When the pivalate was changed to *i*-butyrate, the yield of **3A** decreased (31% yield, Entry 3), and a further change to acetate shut down the reaction. In the case of the reactions using carbonate, tosylate, and phosphate, product **3A** was formed in moderate yields (Entries 4–6). Switching from a ketone to an ester system, when ester **1B** (2.0 equiv) was reacted with pivalate, coupling product **3B** was produced only in 11% yield (Entry 7). Surprisingly, when **1B** was reacted with aryl carbamate, **3B** was produced in good yield (63% NMR yield and 47% isolated yield, Entry 8). In contrast, *i*-butyrate, carbonate, and tosylate gave inferior results (Entries 9–12).

Table 1. Reactivity trend of phenol derivatives in Ni-catalyzed α -arylation of carbonyls^a

Entry	Carbonyls	Ar-OR	Yield of 3 / % ^b
1		pivalate	98 (91)^c
2		carbamate	(77) ^c
3 ^e		<i>i</i> -butyrate	31
4		carbonate	49
5		tosylate	43
6	1A	phosphate	49
7 ^d		pivalate	11
8 ^d		carbamate	63 (47)^c
9 ^{d,e}		<i>i</i> -butyrate	7
10 ^d		carbonate	46
11 ^d		tosylate	24
12 ^{d,e}	1B	phosphate	36
13 ^e		pivalate	(76) ^c
14		carbamate	76
15		<i>i</i> -butyrate	9
16		carbonate	–
17	1C	tosylate	40
18 ^e		phosphate	24

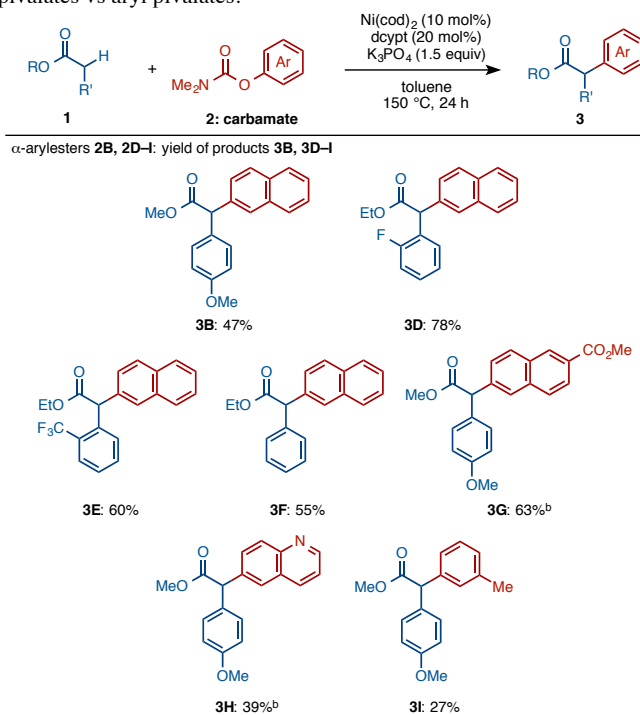
2: Ar-OR



^a Conditions: **1** (0.45 mmol), **2** (0.3 mmol), Ni(cod)₂ (0.03 mmol), dcypT (0.06 mmol), K₃PO₄ (0.45 mmol), toluene (1.2 mL), 150 °C, 24 h. ^b NMR yield. ^c Isolated yield. ^d **1B** (0.60 mmol) was used. ^e Ni(cod)₂ (0.015 mmol) and dcypT (0.015 mmol) were used.

When amide **1C** was used as a carbonyl substrate, both pivalate and carbamate reacted smoothly (Entries 13 and 14), whereas other arylating reagents were much less reactive (Entries 15–18). Although we further tried to optimize other parameters such as ligands, bases, temperature, and solvents, we did not get significantly superior conditions.¹⁰ Thus, with an appropriate choice of arylation agents, the α -arylation of esters and amides with phenol derivatives can now be realized by Ni(cod)₂/dcypT catalyst. Aryl carbamate is a general arylating agent applicable to all of the tested carbonyls and aryl pivalate is a somewhat better reagent in the case of amide arylation.

Next, we examined the coupling reactions of various esters and *O*-arylcabamates **2** (Scheme 2). When the aryl group on the α -position of the ester was changed from *p*-methoxyphenyl to *o*-fluorophenyl, *o*-trifluoromethylphenyl, and phenyl, the corresponding products **3D–3I** were obtained in moderate to good yields.¹¹ Functional groups such as ester (in **3G**) and basic nitrogen atom (in **3H**) were tolerated well under the present coupling conditions. However, the reactions of simple phenol derivatives, instead of naphthol derivatives, gave the corresponding coupling product in low yield. For example, **1B** was coupled with *m*-tolyl dimethylcarbamate to afford the product **3I** in 27% yield. The intermediacy of Meisenheimer complex or η^2 -coordination perhaps accounts for the higher reactivity of naphthyl pivalates vs aryl pivalates.^{7c}

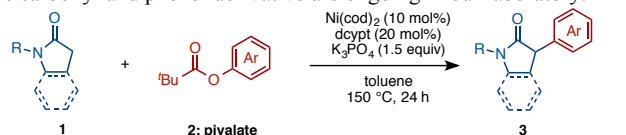


Scheme 2. Arylation of esters with *O*-arylcabamates. ^a Conditions: **1** (0.60 mmol), **2** (0.3 mmol), Ni(cod)₂ (0.03 mmol), dcypT (0.06 mmol), K₃PO₄ (0.45 mmol), toluene (1.2 mL), 150 °C, 24 h. ^b Ni(cod)₂ (0.015 mmol) and dcypT (0.015 mmol) were used.

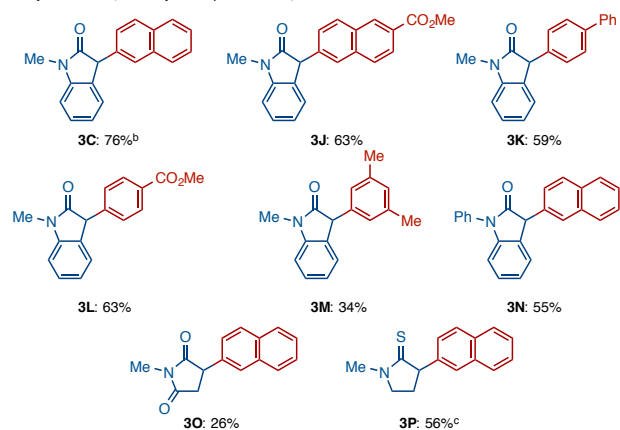
We also investigated the α -arylation of amides with *O*-arylpivalates (Scheme 3). In addition to naphthol-based pivalates, phenol derivatives can also be used as arylating agents, as exemplified by the synthesis of **3K** and **3L**. The use of electron-rich phenol derivatives resulted in low yield (for example, **3M**). Last but not least, our preliminary substrate screening identified that, in addition to oxindole derivatives, succinimide and thioamide derivatives can also be arylated under the influence of Ni(cod)₂/dcypT catalyst to give the coupling products (**3O** and **3P**).¹¹

The present study not only shows the broad applicability of our unique nickel catalyst (Ni-dcypT) in C–H/C–O activation/coupling processes, but also represents the first demonstration of Ni-catalyzed α -arylation of esters and amides with *O*-arylpivalates or *O*-arylcabamates. Various synthetically useful α -aryl esters and amides can now be synthesized from non-halogenated arylating agents through the agency

of Ni-dcypyl catalysis. Mechanistic studies as well as further modifications of the nickel catalyst to achieve a broader scope for both the carbonyl and phenol derivative are ongoing in our laboratory.



α -arylamides **1C**, **1J**–**P**: yield of products **3C**, **3J**–**P**



Scheme 3 Arylation of amides with *O*-aryl pivalates. ^a Conditions: **1** (0.45 mmol), **2** (0.3 mmol), Ni(cod)₂ (0.03 mmol), dcypyl (0.06 mmol), K₃PO₄ (0.45 mmol), toluene (1.2 mL), 150 °C, 24 h. ^b Ni(cod)₂ (0.015 mmol) and dcypyl (0.015 mmol) were used. ^c Naphthalen-2-yl dimethylcarbamate (0.3 mmol) was used instead of **2** and 1,2-bis(dicyclohexylphosphino)ethane (dcype) was used as ligand.

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Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, and ¹H and ¹³C NMR spectra for products. See DOI: 10.1039/c000000x/

Notes and references

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10. See the Supporting Information for details.
11. The reactions gave mono-arylation products as main products, but we also detected small amounts of diarylation products in the reaction mixture.