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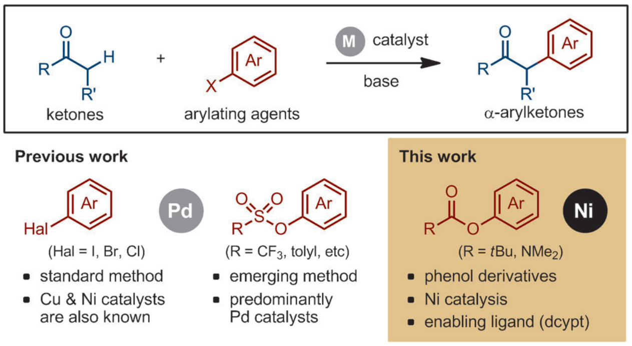
C–O Activation

Nickel-Catalyzed α-Arylation of Ketones with Phenol Derivatives**

Ryosuke Takise, Kei Muto, Junichiro Yamaguchi, and Kenichiro Itami**

Abstract: *The nickel-catalyzed α-arylation of ketones with readily available phenol derivatives (esters and carbamates) provides access to useful α-arylketones. For this transformation, 3,4-bis(dicyclohexylphosphino)thiophene (dcypt) was identified as a new, enabling, air-stable ligand for this transformation. The intermediate of an assumed C–O oxidative addition was isolated and characterized by X-ray crystal-structure analysis.*

The palladium-catalyzed α-arylation of carbonyl compounds with aryl halides or pseudohalides is of great importance in organic synthesis, as the resulting α-aryl carbonyl compounds form the core structures of pharmaceuticals, natural products, and organic materials.[1] After the independent discovery of intermolecular α-arylation of ketones with aryl halides by the groups of Miura, Buchwald, and Hartwig,[2] significant progress has been made in this field. For example, the applicable carbonyl substrates have been expanded to esters, amides, and aldehydes, and the development of improved catalysts and ligands continues to evolve at a rapid pace.[1a] The most commonly employed conditions require haloarenes as arylating agents along with Pd catalysts (Scheme 1). Cu-[3] and Ni-catalyzed[4] α-arylation reactions of carbonyl compounds with haloarenes have also been reported. The use of phenol derivatives as arylating agents is of great importance, because it avoids the requirement for halogenated starting materials and the subsequent generation of halogen-containing waste, and because phenols are usually less expensive and more readily available than haloarenes. In addition, compared with haloarenes, phenols constitute completely different chemical feedstock, including a number of naturally occurring molecules. Although Pd- or Ni-catalyzed α-arylation reactions using sulfonates of phenols (Ar-OSO_2R, in which R = CF_3, *p*-tolyl, methyl, and imidazolyl) have been reported recently (Scheme 1),[5,6] this mode of activation generates a considerable amount of sulfur-containing waste. Herein, we report the first α-arylation of ketones with readily available phenol derivatives, such as aryl pivalates and carbamates (Ar-OCOR with R = *t*Bu, NMe_2), by employing a unique Ni catalyst.



Scheme 1. Catalytic α-arylation of ketones producing useful α-arylketones.

During our development of Ni-catalyzed C–H coupling reactions,[7,8] we discovered a Ni-catalyzed C–H/C–O coupling of azoles and phenol derivatives, which was highly dependent on the choice of the ligand for the effective activation of C–H and C–O bonds in these substrates.[7c,9,10] This reaction necessitates the use of 1,2-bis(dicyclohexylphosphino)ethane (dcype) as ligand. Being aware of the aforementioned challenges in α-arylation chemistry, we then hypothesized that the similarity of the pK_a values of ketones and azoles could be translated into a C–H/C–O coupling (α-arylation) of ketones with simple phenol derivatives using an appropriate Ni catalyst. To this end, we screened catalysts for the α-arylation of ketones with phenol derivatives by varying the ligand on nickel (Table 1).

We evaluated the efficacy of catalysts (ligands) by the reaction of 2-phenylacetophenone (**1A**) and naphthalen-2-yl pivalate (**2a**) to produce the corresponding α-arylation product **3Aa**. In early studies, we identified dcype as superior ligand compared with other ligands such as PCy_3, dppf, and N-heterocyclic carbenes in the present α-arylation.[11] For example, when a mixture of **1A** (1.5 equiv), **2a** (1.0 equiv), and K_3PO_4 (1.5 equiv) in toluene was heated at 150 °C in the presence of $[Ni(dcype)(CO)_2]$[7d,12] (10 mol %), **3Aa** was produced in 25 % yield (Table 1, entry 1). We next examined the effect of cycloalkyl groups in the ligand structure (cyclobutyl, **L1**; cyclopentyl, **L2**; cycloheptyl, **L3**), which resulted in

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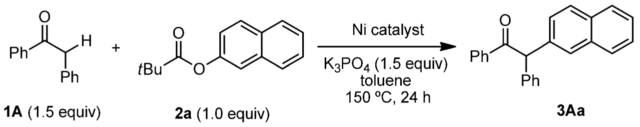
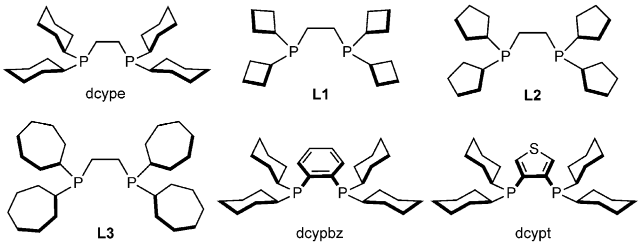
Table 1: Ni-catalyzed α-arylation of **1A** with **2a**; screening of catalysts.[a]



Entry	Ni catalyst (mol %)	Yield of **3Aa** [%][b]
1	$[Ni(dcype)(CO)_2]$ (10)	25
2	$[Ni(\mathbf{L1})(CO)_2]$ (10)	61
3	$[Ni(\mathbf{L2})(CO)_2]$ (10)	30
4	$[Ni(\mathbf{L3})(CO)_2]$ (10)	18
5	$[Ni(dcypbz)(CO)_2]$ (10)	46
6	$[Ni(dcypt)(CO)_2]$ (10)	79
7	$[Ni(cod)_2]$/dcypt (10)[c]	98 (91)[d]
8	$[Ni(cod)_2]$/dcypt (10)[e]	92
9	$[Ni(cod)_2]$/dcypt (5)[c]	95
10	$[Ni(cod)_2]$/dcypt (1)[c]	59
11[f]	$[Ni(cod)_2]$/dcypt (10)[c]	92
12	$[NiCl_2(PPh_3)_2]$/dcypt (10)[c]	66

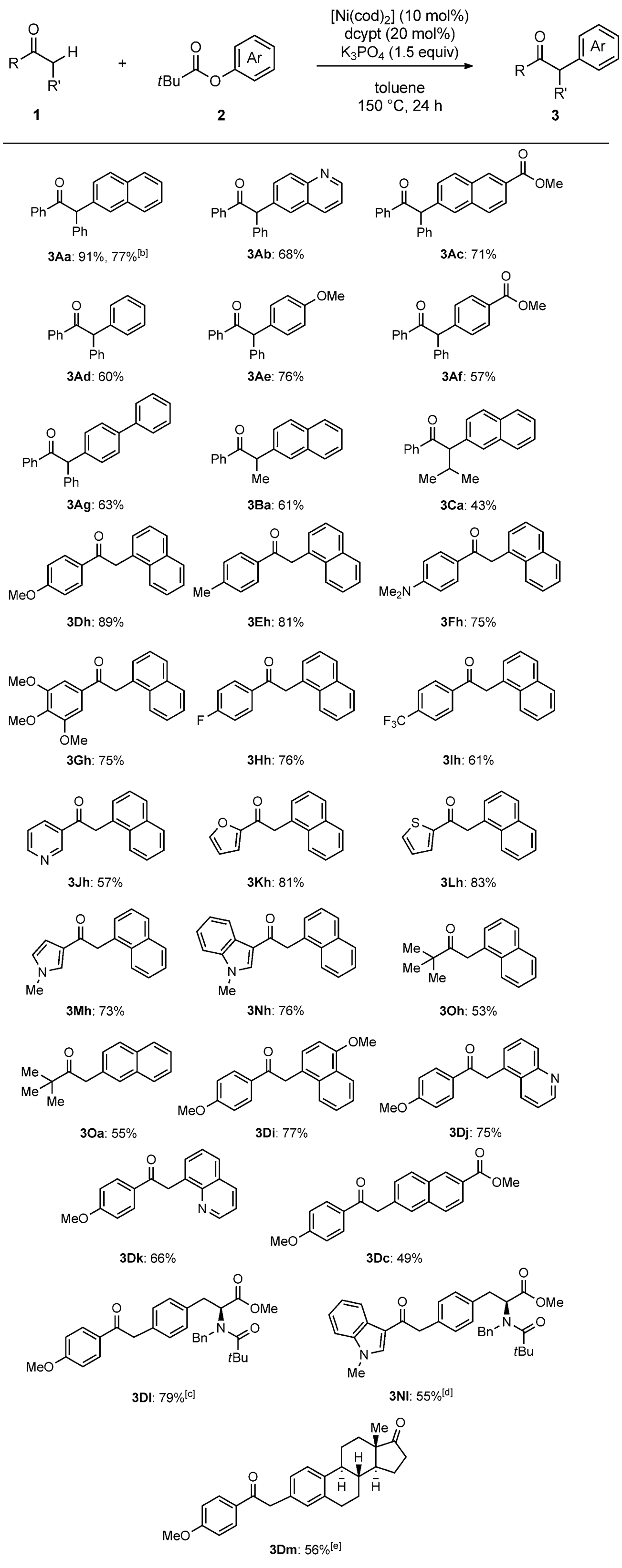
[a] Unless otherwise noted, the reaction conditions were as follows: **1A** (0.45 mmol), **2a** (0.3 mmol), Ni source (0.03 mmol), ligand (0.03 mmol), K_3PO_4 (0.45 mmol), toluene (1.2 mL), 150 °C, 24 h. [b] Yield of **3Aa** was determined by NMR analysis. [c] Ni/ligand = 1:2. [d] Yield of isolated product. [e] Ni/ligand = 1:1. [f] The reaction was conducted at 100 °C for 96 h.



varying yields of **3Aa** (entries 2–4). The use of cyclobutyl analogue **L1** was promising at this stage, but we later found that there is a lack of substrate generality with this ligand.[13] Next, the ethylene linker of dcype was changed to benzene and thiophene bridges (entries 5 and 6). To our delight, the use of thiophene-bridged diphosphine ligand (dcypt) gave the best yields (79 %, entry 6). Interestingly, we found that the catalyst prepared in situ from $[Ni(cod)_2]$ (cod = 1,5-cyclooctadiene) and dcypt gave even better results. For example, in the presence of 10 mol % $[Ni(cod)_2]$ and 20 mol % dcypt, **3Aa** was obtained in 98 % yield (91 % yield of isolated product, entry 7). The ratio of Ni/dcypt (1:2) can be modified (1:1, entry 8), and the reaction proceeded well even when the amount of catalyst is lowered to 5 mol % (entry 9). At a Ni loading of 1 mol %, the product yield suffered, but not tremendously (59 %, entry 10). A reaction temperature of 100 °C sufficed, but longer reaction times were required (entry 11). Furthermore, air-stable $[NiCl_2(PPh_3)_2]$ could also be used as a nickel precursor, albeit with slightly decreased yield (66 %, entry 12). It should be emphasized that unlike dcype and other related ligands, the thiophene-bridged dcypt ligand is an air-stable solid.

With optimal conditions in hand, we examined the substrate scope of the α-arylation of various ketones and phenol derivatives catalyzed by $[Ni(cod)_2]$/dcypt (Table 2).

Table 2: Substrate scope.[a]



3Aa: 91%, 77%[b]
3Ab: 68%
3Ac: 71%
3Ad: 60%
3Ae: 76%
3Af: 57%
3Ag: 63%
3Ba: 61%
3Ca: 43%
3Dh: 89%
3Eh: 81%
3Fh: 75%
3Gh: 75%
3Hh: 76%
3Ih: 61%
3Jh: 57%
3Kh: 81%
3Lh: 83%
3Mh: 73%
3Nh: 76%
3Oh: 53%
3Oa: 55%
3Di: 77%
3Dj: 75%
3Dk: 66%
3Dc: 49%
3Dl: 79%[c]
3Nl: 55%[d]
3Dm: 56%[e]

[a] Unless otherwise noted, the reaction conditions were as follows: **1A** (0.45 mmol), **2a** (0.3 mmol), $[Ni(cod)_2]$ (0.03 mmol), dcypt (0.06 mmol), K_3PO_4 (0.45 mmol), toluene (1.2 mL), 150 °C, 24 h. [b] Naphthalen-2-yl dimethylcarbamate (**2a′**; 0.3 mmol) was used. [c] 4-Methoxyacetophenone (**2D**; 0.6 mmol) was used. [d] 3-Acetyl-1-methylindole (**1N**; 0.5 mmol), (*S*)-4-(2-(*N*-benzylpivalamido)-3-methoxy-3-oxopropyl)phenyl pivalate (**2l**; 0.25 mmol), $[Ni(cod)_2]$ (0.025 mmol), dcypt (0.05 mmol), K_3PO_4 (0.38 mmol), toluene (1.0 mL), 150 °C, 24 h. [e] **2D** (1.2 mmol) was used.

When the reaction was conducted with naphthalen-2-yl dimethylcarbamate (**2a′**) instead of the corresponding pivalate **2a**, the resulting product **3Aa** was obtained in 77% yield. A broad range of phenol pivalates, such as those derived from 6-quinolinol **2b**, 6-methoxycarbonyl-2-naphthol **2c**, phenol **2d**, and 4-functionalized phenols (methoxy **2e**, ester **2f**, and phenyl **2g**), could be coupled with **1A** to afford the corresponding α-arylation products **3Ab**–**3Ag** in good yields.

Ketones for which the substituent on the α-position was changed from phenyl to methyl (**1B**) and isopropyl (**1C**) gave the desired products **3Ba** and **3Ca** in moderate yields. Acetophenone derivatives with a functional group at the C4 position, such as 4-methoxy- (**1D**), 4-methyl- (**1E**), 4-dimethylamino- (**1F**), 3,4,5-trimethoxy- (**1G**), 4-fluoro- (**1H**), and 4-trifluoromethylacetophenone (**1I**), were coupled with naphthalen-1-yl pivalate (**2h**) to furnish the expected products **3Dh**–**3Ih** in good to excellent yields. Heteroarylketones based on pyridine (**1J**), furan (**1K**), thiophene (**1l**), pyrrole (**1M**), and indole (**1N**) were tolerated. Aliphatic ketone **1O** was successfully coupled with arylpivalates **2h** and **2a** to give the corresponding products **3Oh** and **3Oa** in moderate yields. Other examples include the coupling of ketone **1D** with various arylpivalates to give products **3Di**, **3Dj**, **3Dk**, and **3Dc**. Notably, the coupling reaction was also successful with complex phenol derivatives, such as amino acid **2l** and estrone **2m**.

To shed light on the reaction mechanism of this Ni-catalyzed α-arylation, we carried out experiments to identify key intermediates. Recently, we reported the first isolation, structure, and reactivity of an arylnickel(II) pivalate that bears the dcype ligand, which was obtained by the oxidative addition of an aryl C–O bond to a nickel complex.[7f] Similarly, we attempted to isolate the Ni/dcypt complex shown in Figure 1a. The stoichiometric reaction of naphthalen-2-yl pivalate (**2a**, 1.0 equiv) with [Ni(cod)$_2$] (1.0 equiv) and dcypt (1.0 equiv) in toluene at 100°C successfully gave arylnickel(II) pivalate complex **4** in 77% yield of isolated product. It should be noted that the oxidative addition of **2a** to Ni/dcypt is faster than that to Ni/dcype (dcypt: 2 h, dcype: 8 h at 100°C, confirmed by ^{1}H NMR analysis). This observation correlates to an enhanced reactivity and increased yield of coupling products in the Ni/dcypt system.

The structure of **4** was confirmed by X-ray crystallographic analysis (Figure 1b). The X-ray crystal structure showed that the nickel atom is in a square-planar arrangement surrounded by two phosphines, a carbon atom, and an oxygen atom. The dcypt ligand was coordinated to the nickel atom in a *cis* configuration, as expected. These results clearly show that the C–O oxidative addition of **2a** to Ni^0 takes place under the conditions similar to those employed in catalytic reactions.

As a part of our studies to investigate the reactivity of complex **4** in oxidative additions, we next examined stoichiometric and catalytic reactions of **4** to produce the expected α-arylation product (Scheme 2). When **4** was treated with stoichiometric amounts of **1A** and K$_3$PO$_4$ at 120°C in toluene, the α-arylation product **3Aa** was obtained in 50% yield. Similarly, **3Aa** was obtained in 82% yield when **4** was used as a catalyst (10 mol%). These results are completely consistent with complex **4** operating as the catalyst, as well as one of the intermediates in the catalytic cycle. It is also of note that the presence of a base is critical for this α-arylation reaction.

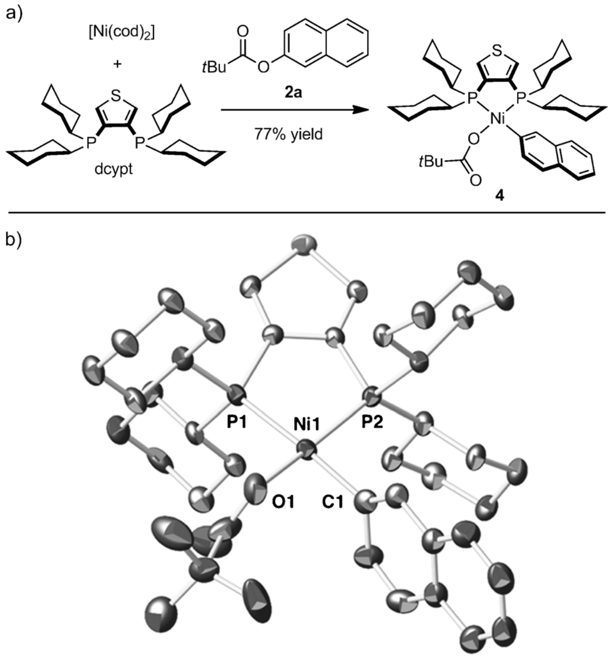
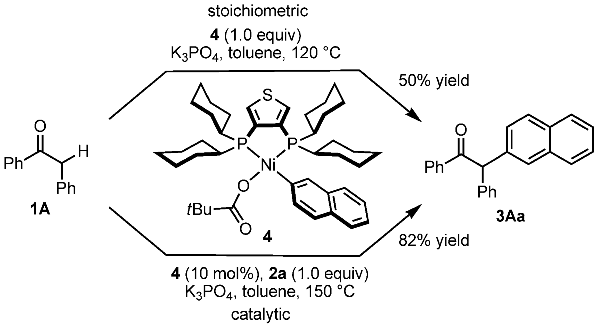
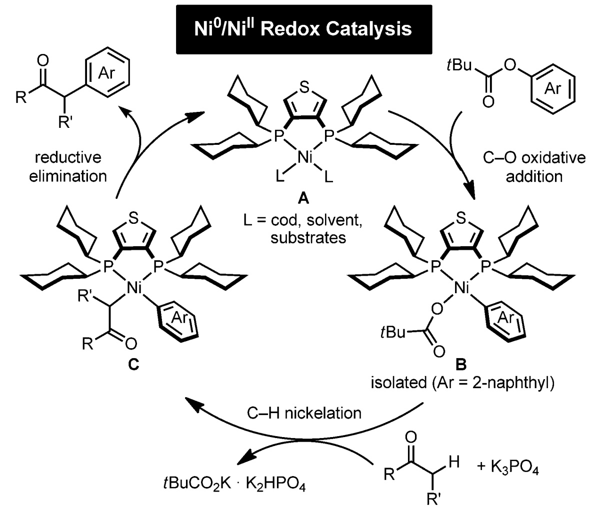


Figure 1. a) Synthesis of arylnickel(II) pivalate complex **4**. b) ORTEP representation of one of two independent molecules of **4**. Hydrogen atoms are omitted for clarity; thermal ellipsoids are drawn at 50% probability. Selected bond lengths [Å] and angles [deg]: Ni1–P1 = 2.2242(14), Ni1–O1 = 1.946(4), Ni1–P2 = 2.1364(14) Ni1–C1 = 1.912(5), P1-Ni-P2 = 90.91(5), P2-Ni1-C1 = 89.97(15), P1-Ni1-C1 = 174.27(16), P2-Ni1-O1 = 165.49(15), P1-Ni1-O1 = 94.51(12), O1-Ni1-C1 = 85.99(18).



Scheme 2. Stoichiometric and catalytic α-arylation with **4**.

Taking all these experimental data into consideration, we propose a mechanism for this α-arylation reaction as shown in Scheme 3. The reaction proceeds by a Ni^0/Ni^{II} redox catalytic cycle, consisting of 1) CO oxidative addition of phenol derivative (Ar–OR) onto Ni^0/dcypt complex **A** to form an Ar–Ni–OR complex **B** (which is identical to complex **4**), 2) C–H nickelation of a ketone with base to yield diorganonickel(II) complex **C**, and 3) reductive elimination of the coupling product **3** and regeneration of Ni^0 species **A**.



Scheme 3. A plausible reaction mechanism.

In summary, we have developed the first α-arylation of ketones with readily available phenol derivatives (esters and carbamates) employing Ni catalysts to give useful α-arylketones without producing halogen- or sulfur-containing waste. The air-stable 3,4-bis(dicyclohexylphosphino)thiophene (dcypt) was discovered as an enabling ligand for this transformation. A plausible Ni^0/Ni^{II} catalytic cycle consisting of C–O oxidative addition, C–H nickelation, and reductive elimination was supported by the stoichiometric reaction that gave the C–O oxidative addition complex and its stoichiometric and catalytic reactions furnishing the corresponding α-arylation product. The successful applications to complex molecules such as amino acid and estrone shows the potential of the present reaction. Further developments in C–H and C–O bond activation,[9,10] and the design of a new ligand are ongoing in our laboratory.

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Keywords: α-arylation · C–O activation · nickel · oxidative addition · synthetic methods

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[11] See the Supporting Information for details.

[12] This complex (CAS No. 141974-66-5) is currently commercially available from Kanto Chemicals Co. (Product No. 08470-55).

[13] When acetophenone was used as a substrate, the α-arylation product was obtained only in 6% yield (see the Supporting Information).

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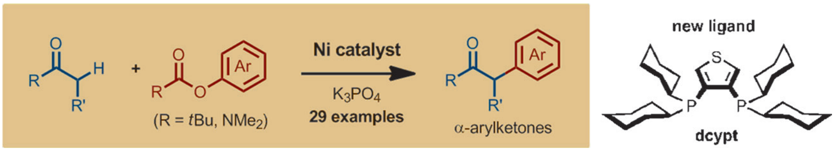

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