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## Ni-Catalyzed $\alpha$ -arylation of esters and amides with phenol derivatives<sup>†</sup>

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**A nickel-catalyzed  $\alpha$ -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)<sub>2</sub>, 3,4-bis(dicyclohexylphosphino)thiophene (dcypt), and K<sub>3</sub>PO<sub>4</sub>, various esters and amides undergo  $\alpha$ -arylation with *O*-arylpivalates or *O*-arylcarbamates to afford the corresponding coupling products. The thus obtained  $\alpha$ -aryl esters and amides are useful precursors of privileged motifs such as  $\alpha$ -arylcarboxylic acids and  $\beta$ -arylamines.**

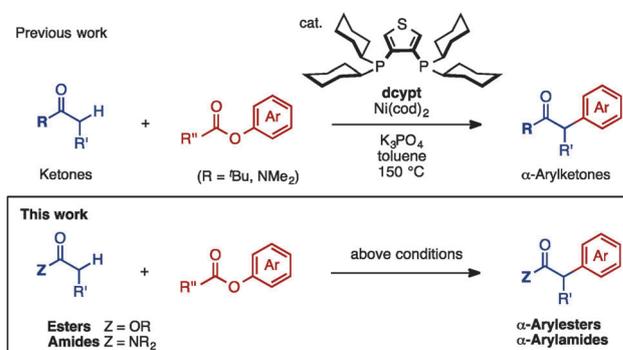
$\alpha$ -Aryl esters and amides are useful intermediates in organic synthesis that can be converted into prevalent motifs such as  $\alpha$ -arylcarboxylic acids and  $\beta$ -arylamines.<sup>1</sup> Therefore, over the last two decades, significant efforts have been devoted to develop concise, direct, and environmental friendly methods constructing these privileged motifs. A representative method for the synthesis of  $\alpha$ -aryl esters and amides is the Pd-catalyzed  $\alpha$ -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 pioneers in this field.<sup>2,3</sup> However, these state-of-the-art  $\alpha$ -arylation reactions typically necessitate expensive Pd catalysts as well as haloarenes as arylating agents.<sup>4,5</sup> Herein, we report that our unique nickel catalyst allows the  $\alpha$ -arylation of esters and amides with phenol derivatives as arylating agents and K<sub>3</sub>PO<sub>4</sub> 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.<sup>6,7</sup> 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)<sub>2</sub> (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.<sup>8</sup>

Very recently, we translated the established nickel-based C–H/C–O activation mode to  $\alpha$ -arylation of ketones with phenol derivatives (*O*-arylpivalates or *O*-arylcarbamates), which addresses some of the drawbacks in the state-of-the-art  $\alpha$ -arylation chemistry (Scheme 1).<sup>9</sup> 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)<sub>2</sub>/dcypt catalyst can be applied to a more challenging class of substrates, esters and amides, in  $\alpha$ -arylation chemistry.

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 a Ni(cod)<sub>2</sub>/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



Scheme 1 Ni-catalyzed  $\alpha$ -arylation of carbonyl compounds.

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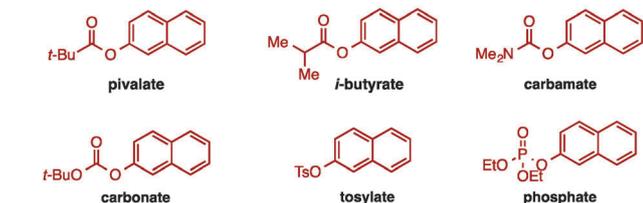
<sup>†</sup> Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and <sup>1</sup>H and <sup>13</sup>C NMR spectra of products. See DOI: 10.1039/c4cc08426h

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**Table 1** Reactivity trend of phenol derivatives in Ni-catalyzed  $\alpha$ -arylation of carbonyls<sup>a</sup>

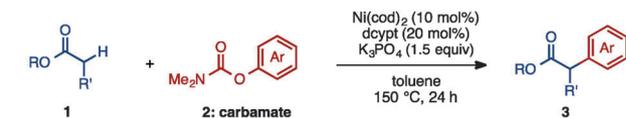
| Entry             | Carbonyls | Ar-OR      | Yield of 3 <sup>b</sup> /% |
|-------------------|-----------|------------|----------------------------|
| 1                 |           | Pivalate   | 98 (91) <sup>c</sup>       |
| 2                 |           | Carbamate  | (77) <sup>c</sup>          |
| 3 <sup>e</sup>    |           | i-Butyrate | 31                         |
| 4                 |           | Carbonate  | 49                         |
| 5                 |           | Tosylate   | 43                         |
| 6                 |           | Phosphate  | 49                         |
| 7 <sup>d</sup>    |           | Pivalate   | 11                         |
| 8 <sup>d</sup>    |           | Carbamate  | 63 (47) <sup>c</sup>       |
| 9 <sup>d,e</sup>  |           | i-Butyrate | 7                          |
| 10 <sup>d</sup>   |           | Carbonate  | 46                         |
| 11 <sup>d</sup>   |           | Tosylate   | 24                         |
| 12 <sup>d,e</sup> |           | Phosphate  | 36                         |
| 13 <sup>e</sup>   |           | Pivalate   | (76) <sup>c</sup>          |
| 14                |           | Carbamate  | 76                         |
| 15                |           | i-Butyrate | 9                          |
| 16                |           | Carbonate  | —                          |
| 17                |           | Tosylate   | 40                         |
| 18 <sup>e</sup>   |           | Phosphate  | 24                         |



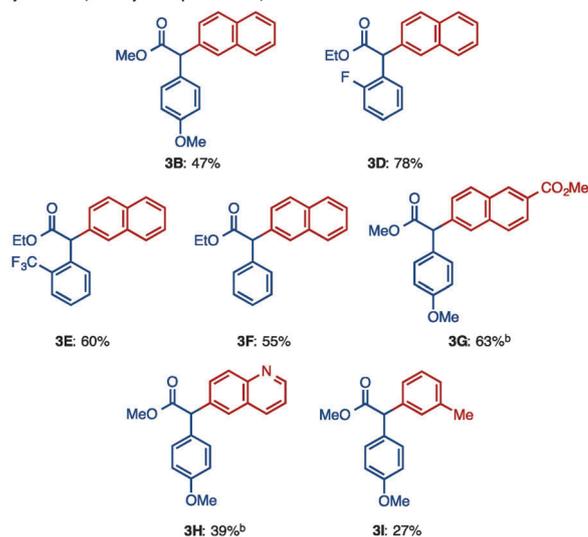
<sup>a</sup> Conditions: **1** (0.45 mmol), **2** (0.3 mmol), Ni(cod)<sub>2</sub> (0.03 mmol), dcpyt (0.06 mmol), K<sub>3</sub>PO<sub>4</sub> (0.45 mmol), toluene (1.2 mL), 150 °C, 24 h. <sup>b</sup> NMR yield. <sup>c</sup> Isolated yield. <sup>d</sup> **1B** (0.60 mmol) was used. <sup>e</sup> Ni(cod)<sub>2</sub> (0.015 mmol) and dcpyt (0.015 mmol) were used.

Ni(cod)<sub>2</sub> (10 mol%), dcpyt (20 mol%), and K<sub>3</sub>PO<sub>4</sub> (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).<sup>9</sup> When the pivalate was changed to i-butyrate, the yield of **3A** decreased (31% yield, entry 3), and a further change to acetate shuts 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, the 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).

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.<sup>10</sup> Thus, with an appropriate choice of arylation agents,



$\alpha$ -arylesters **2B**, **2D–I**: yield of products **3B**, **3D–I**



**Scheme 2** Arylation of esters with *O*-arylcaramates. <sup>a</sup> Conditions: **1** (0.60 mmol), **2** (0.3 mmol), Ni(cod)<sub>2</sub> (0.03 mmol), dcpyt (0.06 mmol), K<sub>3</sub>PO<sub>4</sub> (0.45 mmol), toluene (1.2 mL), 150 °C, 24 h. <sup>b</sup> Ni(cod)<sub>2</sub> (0.015 mmol) and dcpyt (0.015 mmol) were used.

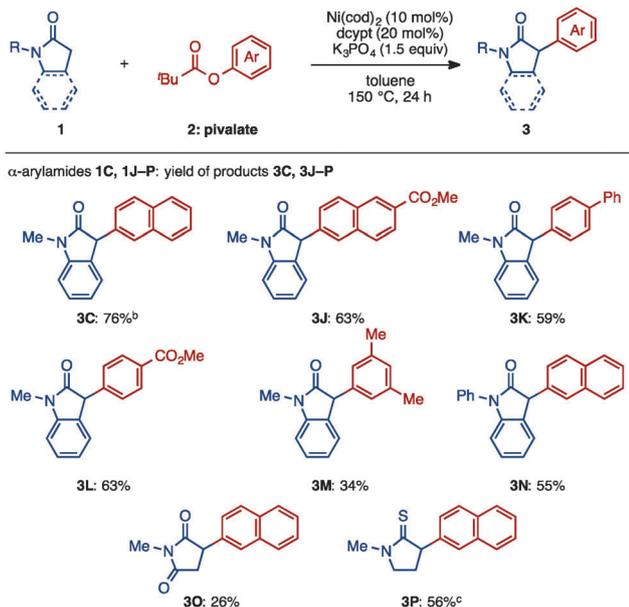
the  $\alpha$ -arylation of esters and amides with phenol derivatives can now be realized by a Ni(cod)<sub>2</sub>/dcpyt catalyst. Aryl carbamate is a general arylating agent applicable to all of the tested carbonyls and aryl pivalate is a somewhat better reagent in the case of amide arylation.

Next, we examined the coupling reactions of various esters and *O*-arylcaramates **2** (Scheme 2). When the aryl group on the  $\alpha$ -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.<sup>11</sup> Functional groups such as ester (in **3G**) and the 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 the Meisenheimer complex or  $\eta^2$ -coordination perhaps accounts for the higher reactivity of naphthyl pivalates vs. aryl pivalates.<sup>7e</sup>

We also investigated the  $\alpha$ -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 the Ni(cod)<sub>2</sub>/dcpyt catalyst to give the coupling products (**3O** and **3P**).<sup>11</sup>

The present study not only shows the broad applicability of our unique nickel catalyst (Ni-dcpyt) in C–H/C–O activation/coupling





**Scheme 3** Arylation of amides with *O*-arylpivalates. <sup>a</sup> Conditions: **1** (0.45 mmol), **2** (0.3 mmol),  $\text{Ni}(\text{cod})_2$  (0.03 mmol), dcypt (0.06 mmol),  $\text{K}_3\text{PO}_4$  (0.45 mmol), toluene (1.2 mL), 150 °C, 24 h. <sup>b</sup>  $\text{Ni}(\text{cod})_2$  (0.015 mmol) and dcypt (0.015 mmol) were used. <sup>c</sup> Naphthalen-2-yl dimethylcarbamate (0.3 mmol) was used instead of **2** and 1,2-bis(dicyclohexylphosphino)ethane (dcype) was used as a ligand.

processes, but also represents the first demonstration of Ni-catalyzed  $\alpha$ -arylation of esters and amides with *O*-arylpivalates or *O*-arylcabamates. Various synthetically useful  $\alpha$ -aryl esters and amides can now be synthesized from non-halogenated arylating agents through the agency of Ni-dcypt catalysis. Mechanistic studies as well as further modifications of the nickel catalyst to achieve a broader scope for both the carbonyl and phenol derivatives are ongoing in our laboratory.

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## Notes and references

- 1 For selected reviews and accounts, see: (a) F. Bellina and R. Rossi, *Chem. Rev.*, 2010, **110**, 1082; (b) C. C. C. Johansson and T. J. Colacot,

*Angew. Chem., Int. Ed.*, 2010, **49**, 676; (c) P. Novák and R. Martin, *Curr. Org. Chem.*, 2011, **15**, 3233; (d) D. A. Culkin and J. F. Hartwig, *Acc. Chem. Res.*, 2003, **36**, 234.

- 2 For representative reports on Pd-catalyzed  $\alpha$ -arylation of esters with haloarenes, see: (a) T. Satoh, J. Inoh, Y. Kawamura, Y. Kawamura, M. Miura and M. Nomura, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 2239; (b) W. A. Moradi and S. L. Buchwald, *J. Am. Chem. Soc.*, 2001, **123**, 7996; (c) S. Lee, N. A. Beare and J. F. Hartwig, *J. Am. Chem. Soc.*, 2001, **123**, 8410; (d) M. Jørgensen, S. Lee, X. Liu, J. P. Wolkowski and J. F. Hartwig, *J. Am. Chem. Soc.*, 2002, **124**, 12557; (e) O. Gaertzen and S. L. Buchwald, *J. Org. Chem.*, 2002, **67**, 465; (f) N. A. Beare and J. F. Hartwig, *J. Org. Chem.*, 2002, **67**, 541; (g) D. Sole and O. Serrano, *J. Org. Chem.*, 2008, **73**, 2476; (h) E. A. Bercot, S. Caille, T. M. Bostick, K. Ranganathan, R. Jensen and M. M. Faul, *Org. Lett.*, 2008, **10**, 5251; (i) T. Hama and J. F. Hartwig, *Org. Lett.*, 2008, **10**, 1545; (j) T. Hama and J. F. Hartwig, *Org. Lett.*, 2008, **10**, 1549; (k) L. Jiang, S. Weist and S. Jansat, *Org. Lett.*, 2009, **11**, 1543.
- 3 For representative reports on Pd-catalyzed  $\alpha$ -arylation of amides with haloarenes, see: (a) K. H. Shaughnessy, B. C. Hamann and J. F. Hartwig, *J. Org. Chem.*, 1998, **63**, 6546; (b) S. Lee and J. F. Hartwig, *J. Org. Chem.*, 2001, **66**, 3402; (c) T. Hama, D. A. Culkin and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 4976; (d) Y.-X. Jia, J. M. Hillgren, E. L. Watson, S. P. Marsden and E. P. Kündig, *Chem. Commun.*, 2008, 4040; (e) M. J. Durbin and M. C. Willis, *Org. Lett.*, 2008, **10**, 1413; (f) A. M. Taylor, R. A. Altman and S. L. Buchwald, *J. Am. Chem. Soc.*, 2009, **131**, 9900; (g) L. Ackermann, R. Vicente and N. Hofmann, *Org. Lett.*, 2009, **11**, 4274; (h) B. Zheng, T. Jia and P. J. Walsh, *Adv. Synth. Catal.*, 2014, **356**, 165.
- 4 Few  $\alpha$ -arylation of esters and amides under non-Pd systems, see: (a) D. J. Spielvogel and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 3500; (b) S. F. Yip, H. Y. Cheung, Z. Zhou and F. Y. Kwong, *Org. Lett.*, 2007, **9**, 3469; (c) B. Peng, D. Geerdink, C. Farès and N. Maulide, *Angew. Chem., Int. Ed.*, 2014, **53**, 5462.
- 5 Only one example of Pd-catalyzed  $\alpha$ -arylation of esters with phenol derivatives (aryl tosylates) was reported. H. N. Nguyen, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 11818.
- 6 For reviews, see (a) J. Yamaguchi, K. Muto and K. Itami, *Eur. J. Org. Chem.*, 2013, 19; (b) S. Z. Tasker, E. A. Standley and T. F. Jamison, *Nature*, 2014, **509**, 299; (c) J. Cornella, C. Zarate and R. Martin, *Chem. Soc. Rev.*, 2014, **43**, 8081; (d) B. M. Rosen and K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg and V. Percec, *Chem. Rev.*, 2011, **111**, 1346.
- 7 For selected recent examples of C–O activation, see: (a) M. Tobisu, T. Shimasaki and N. Chatani, *Angew. Chem., Int. Ed.*, 2008, **47**, 4866; (b) D.-G. Yu and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2011, **50**, 7097; (c) K. W. Quasdorf, A. Antoft-Finch, P. Liu, A. L. Silberstein, A. Komaromi, T. Blackburn, S. D. Ramgren, K. N. Houk, V. Snieckus and N. K. Garg, *J. Am. Chem. Soc.*, 2011, **133**, 6352; (d) C. Zarate and R. Martin, *J. Am. Chem. Soc.*, 2014, **136**, 2236; (e) A. Correa, T. León and R. Martin, *J. Am. Chem. Soc.*, 2014, **136**, 1062.
- 8 (a) K. Muto, J. Yamaguchi and K. Itami, *J. Am. Chem. Soc.*, 2012, **134**, 169; (b) K. Amaike, K. Muto, J. Yamaguchi and K. Itami, *J. Am. Chem. Soc.*, 2012, **134**, 13573; (c) L. Meng, Y. Kamada, K. Muto, J. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2013, **52**, 10048; (d) K. Muto, J. Yamaguchi, A. Lei and K. Itami, *J. Am. Chem. Soc.*, 2013, **135**, 16384; (e) H. Xu, K. Muto, J. Yamaguchi, C. Zhao, K. Itami and D. G. Musaev, *J. Am. Chem. Soc.*, 2014, **136**, 14834.
- 9 R. Takise, K. Muto, J. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2014, **53**, 6791.
- 10 See the ESI† 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.

