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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) and \( 3,4 \)-bis(dicyclohexylphosphino)thiophene (dcypt), and \( K_2 \)PO\(_4\), various esters and amides undergo \( \alpha \)-arylation with \( O \)-arylketones 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.\(^1\) 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 \( \alpha \)-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 the pioneers in this field.\(^2,3\) However, these state-of-the-art \( \alpha \)-arylation reactions typically necessitate expensive Pd catalysts as well as haloarenes as arylation agents.\(^4,5\) Herein, we report that our unique nickel catalyst allows the \( \alpha \)-arylation of esters and amides with phenol derivatives as arylation agents and \( K_2 \)PO\(_4\), as a mild base.

In recent years, phenol derivatives have received much attention as green and inexpensive arylation 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); (cod = 1,5-cyclooctadiene) and \( 1,2 \)-bis(dicyclohexylphosphino)ethane (dcypt), 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 \( \alpha \)-arylation of ketones with phenol derivatives (\( O \)-arylketones or \( O \)-arylcarbamates), which addresses some of the drawbacks in the state-of-the-art \( \alpha \)-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 dcypt. 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)/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 Ni(cod)/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 \( K_2 \)PO\(_4\) (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-butrate, 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-butrate, carbonate, and tosylate gave inferior results (Entries 9–12).

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

| Entry | Carbonyls | Ar-OR | Yield of 3 (%)^\text{b} |
|-------|-----------|-------|--------------------------|
| 1     | pivalate  |       | 98 (91)^\text{a}         |
| 2     | carbamate |       | 77^\text{a}              |
| 3     | i-butrate |       | 31                       |
| 4     | carbonate |       | 49                       |
| 5     | tosylate  |       | 43                       |
| 6     | phosphate |       | 49                       |
| 1A    | pivalate  |       | 11                       |
| 1B    | carbamate |       | 63 (47)^\text{a}         |
| 1C    | pivalate  | MeO   | 76                       |
| 1D    | i-butrate | MeO   | 9                        |
| 1E    | carbonate | MeO   | 40                       |
| 1F    | phosphate | MeO   | 24                       |

^a Conditions: 1 (0.45 mmol), 2 (0.3 mmol), Ni(cod), (0.03 mmol), dcyt (0.06 mmol), K$_2$PO$_4$ (0.45 mmol), toluene (1.2 mL), 150 °C, 24 h. ^b Isolated yield. ^c 1B (0.60 mmol) was used. ^d Ni(cod), (0.015 mmol) and dcyt (0.015 mmol) were used.

Next, we examined the coupling reactions of various esters and O-arylcarbamates 2 (Scheme 2). When the aryl group on the α-position of the ester was changed from p-methoxyphenyl to o-fluorophenyl, α-trifluoromethylphenyl, and phenyl, the corresponding products 3D–3I were obtained in moderate to good yields. 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 3J in 27% yield. The intermediacy of Meisenheimer complex or η^3- coordination perhaps accounts for the higher reactivity of naphthyl pivalates vs aryl pivalates.\textsuperscript{7v}

We also investigated the α-arylation of amides with O-aryl pivalates (Scheme 3). In addition to naphthol-based pivalates, phenol derivatives can also be used as arylation 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)/dcypt catalyst to give the coupling products 3O and 3P.\textsuperscript{11}

The present study not only shows the broad applicability of our unique nickel catalyst (Ni-dcyt) 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-aryl pivalates or O-aryl carbamates. Various synthetically useful α-aryl esters and amides can now be synthesized from non-halogenated arylation agents through the agency
of Ni-decyl 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.

Scheme 3 Arylation of amides with O-aryl pivalates. a Conditions: 1 (0.45 mmol), 2 (0.3 mmol), Ni(cod), (0.03 mmol), dcypt (0.06 mmol), KPO4, (0.45 mmol), toluene (1.2 mL), 150 °C, 24 h. b Ni(cod), (0.015 mmol) and dcypt (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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Notes and references
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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. Cuklin and J. F. Hartwig, Acc. Chem. Res., 2003, 36, 234.

2. For representative reports on Pd-catalyzed α-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. F. Paul, 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 α-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. Cuklin 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 α-arylation of ester 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. Fares and N. Maulide, Angew. Chem. Int. Ed., 2014, 53, 5462.

5. Only one example of Pd-catalyzed α-arylation of esters with phenyl 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, K. W. Quasdorff, D. A. Wilson, N. Zhang, A-M. Resneritua, N. K. Garg and V. Percece, 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. Quasdorff, A. Anffo-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. Corea, 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. Amakata, 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 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.