ChemComm

Nickel-Catalyzed Direct Methylation of Arylphosphines via Carbon–Phosphorus Bond Cleavage Using $AlMe_3$

Journal:	*ChemComm*
Manuscript ID	CC-COM-05-2023-002455.R2
Article Type:	Communication

COMMUNICATION

Nickel-Catalyzed Direct Methylation of Arylphosphines via Carbon–Phosphorus Bond Cleavage Using $AlMe_3$

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Takuya Igarashi,[a] Ryoma Shimazumi,[a] Naoto Chatani[a,c] and Mamoru Tobisu*[,a,b]

We report herein on the nickel-catalyzed methylation of arylphosphines using $AlMe_3$ via the cleavage of unactivated C(aryl)–P bonds. This reaction allows for the direct, catalytic substitution of an aryl group on a phosphorus center with a methyl group. This catalytic methylation can proceed, when phosphine oxides and sulfides are used as a substrate.

Triorganophosphines are widely used in organic synthesis, for example, as organocatalysts,[1] deoxygenating agents,[2] and ligands for transition metal complexes,[3] which makes the development of methods for their synthesis a continuingly important research subject. [4] The late-stage conversion of stable, readily available arylphosphines to alkylphosphines represents a particularly a useful technique, to diversify the library of existing organophosphine compounds. In contrast to a number of examples of aryl group exchange reactions of aryphosphines,[5] the conversion of the aryl group in an arylphosphine to an alkyl group has met with limited success in terms of catalysis (Figure 1a). This transformation is typically accomplished via the reductive cleavage of a C(aryl)–P bond using a stoichiometric amount of a strong reducing agent (e.g., Na, Li) to generate a phosphide anion, followed by alkylation by RX (Figure 1a, top).[6] The chromium-catalyzed alkylation of triarylphosphines bearing a directing group using an excess of ArMgX as a reducing agent was also reported recently (Figure 1a, middle).[7] Another strategy for transforming arylphosphines into alkylphosphines involves the prior formation of an alkylphosphonium salt by reaction with an alkyl halide, followed by the selective cleavage of the C(aryl)–P bond (Figure 1a, bottom).[5m,8] Herein, we report on the nickel-catalyzed direct substitution of an aryl group of an arylphosphine by a methyl group using

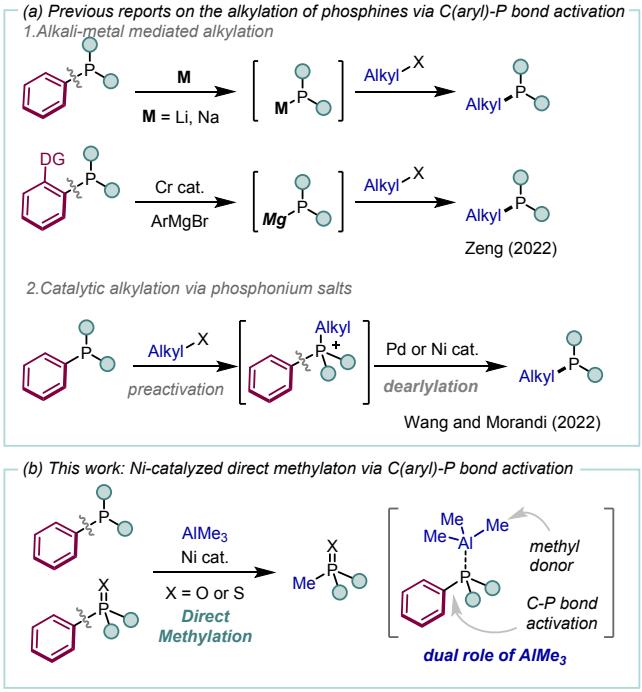


Figure 1 Alkylation of phosphines via the cleavage of C(aryl)-P bond: precedents and this work

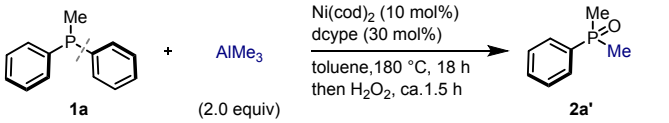
trimethylaluminum ($AlMe_3$) (Figure 1b). The use of $AlMe_3$ as a methylating agent allows for the direct methylation of C(aryl)–P bonds in arylphosphines without the need for a directing group or the prior formation of phosphonium salts.

Our laboratory[9a] and Rueping[9b] recently reported on the nickel-catalyzed alkylation of a C(aryl)–O bond in an aryl ether using a trialkylaluminum reagent. In this reaction, the aluminum reagent presumably acts, not only as an alkyl nucleophile, but also as a Lewis acid, by which C(aryl)–O bond activation by Ni(0) is facilitated by the pre-coordination of an ether oxygen to an aluminum center.[10] We envisioned that the combination of a Ni(0) catalyst and a trialkylaluminum reagent could also be

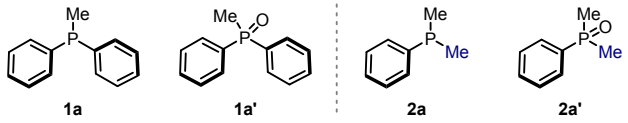
[a.] *Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan*
[b.] *Innovative Catalysis Science Division, Institute for Open and Transdisciplinary Research Initiatives (ICS-OTRI), Osaka University, Suita, Osaka 565-0871, Japan.Address here.*
[c.] *Research Center for Environmental Preservation), Osaka University, Suita, Osaka 565-0871, Japan.Address here.*
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

applied to the alkylation of arylphosphines via the prior formation of a phosphine/aluminum adduct. Based on this hypothesis, we initially examined the nickel-catalyzed reaction of diphenyl(methyl)phosphine (**1a**) with $AlMe_3$ (Table 1). As a result of extensive optimization,[11] it was found that the reaction of **1a** with $AlMe_3$ (2 equiv) in the presence of $Ni(cod)_2$ (10 mol %) and dcype [1,2-bis(dicyclohexylphosphino)ethane, 30 mol %] in toluene at 180 °C for 18 h, followed by quenching with H_2O_2, gave the methylated phosphine oxide **2a'** in 58% GC yield (Entry 1). The double methylated product (*i.e.*, trimethylphosphine oxide) was not observed. The yield was further improved to 76% by slightly decreasing the amount of $AlMe_3$ to 1.8 equiv.[12] The methylation did not proceed in the absence of a nickel catalyst (Entry 2), but the addition of dcype was found to not be essential (Entry 3). This is presumably because the phosphine substrate can also serve as a supporting ligand for Ni(0) in the absence of dcype. The nature of the ligand did not have a profound impact on the efficiency of the reaction of **1a**. For example, the use of monodentate NHC ligands also afforded **2a'** in comparable yields (Entries 4 and 5). Other organometallic methylating reagents, including MeLi and MeMgBr, failed to promote the reaction, while the use of $AlMe_2Cl$ gave **2a'** albeit in a decreased yield of 24% (Entries 6 and 7). When $AlEt_3$ was used instead of $AlMe_3$, no ethylated product was formed and **1a** remained largely unreacted (Entry 8). The reaction can also proceed at a lower temperature of 140 °C, although the yield was slightly decreased (Entry 9). The use of $Ni(OAc)_2$ as nickel(II) catalysts also promoted this reaction with moderate yield (Entry 10). Importantly, this methylation reaction was found to proceed even when the phosphine oxide **1a'** was used as a substrate with the desired product **2a'** being produced in 42% GC yield under identical conditions (Entry 11). Given the availability and air-stability of phosphine oxide derivatives,[13] the direct methylation of these oxides greatly expands the usefulness of this reaction.

Table 1 Optimization of the nickel-catalyzed methylation of **1a**[a]



Entry	Deviation from above conditions	GC yield [%]
1	none	58 (76)[b]
2	without $Ni(cod)_2$/dcype	0
3	without dcype	46
4	IPr·HCl/NaO^{t}Bu instead of dcype	48
5	ICy·HCl/NaO^{t}Bu instead of dcype	42
6	MeLi or MeMgBr instead of $AlMe_3$	0
7	$AlMe_2Cl$ instead of $AlMe_3$	24
8	$AlEt_3$ instead of $AlMe_3$	0[c]
9	140 °C instead of 180 °C	42
10	$Ni(OAc)_2$ instead of $Ni(cod)_2$	50[b]
11	**1a'** insted of **1a**	42[b]



[a]Reaction conditions: phosphine **1** (0.15 mmol), $Ni(cod)_2$ (0.015 mmol), dcype (0.045 mmol) and $AlMe_3$ (0.15 mL) in toluene (0.3 mL) at 180 °C for 18 h. [b]Using 1.8 equiv of $AlMe_3$. [c]Yield of ethylated phosphine.

Having optimized the reaction conditions in hand, we explored the scope of this nickel-catalyzed methylation of arylphosphines (Figure 2). Because of the difficulty in isolating phosphine oxide derivatives by column chromatography due to their high-polarity, the products were routinely isolated in the form of air-stable phosphine sulfides **2"** after workup with S_8.[14] Regarding the alkyl substituents of diphenyl(alkyl)phosphine substrates, a range of primary and secondary alkyl groups were found to be applicable. For example, methylated (**2a"**) and ethylated (**2b"**) phosphine sulfides were formed in 72% and 66% yields, respectively. This reaction also proceeded in the case of substrates bearing bulky groups such as isopropyl (**1c"**) and cyclohexyl (**1d"**), with the corresponding methylated phosphine products being successfully generated. We next examined the scope of the reaction using phosphine oxide and sulfide derivatives as starting materials. In addition to phosphine oxide **1a'**, we found that diphenyl(methyl)phosphine sulfide (**1a"**) can also serve as a viable substrate with the corresponding methylated product **2a"** being formed in 59% yield. In addition, this reaction could be applied to a series of cyclic phosphine sulfide derivatives (i.e, **2e"** and **2f"**), allowing for the late-stage modification of the P-substituent in dibenzophosphole derivatives. The use of $(EtO)PPh_2$ as a substrate under these conditions resulted in the formation of **1a"** (21%) and **2a"** (29%), likely through the generation of $PMePh_2$ (see ESI for details). Triphenylphosphine **4a** can also participate in this catalytic methylation. After numerous optimizations,[15] the methylation proceeded when the reaction was carried out at 120 °C for 24 h using IPr as a ligand with the monomethylated (**5a**) and the dimethylated (**2a"**) products being obtained in 28% and 53% yields, respectively. Introducing methyl groups at the para-positions (*i.e.*, **4b**) had no significant effect on the

reaction efficiency and the corresponding methlylated phosphines **5b** and **2g"** were formed in a similar manner. In contrast, the use of an electron-deficient CF_3-substituted phosphine resulted in no reaction, indicating that the Lewis-basicity of the phosphine is important for the formation of an adduct with $AlMe_3$ (*vide infra*). Bisposphines, such as 1,2-diphenylphosphinoethane and 1,6-diphenylphosphinohexane, failed to afford the corresponding methylated product (see ESI for details).

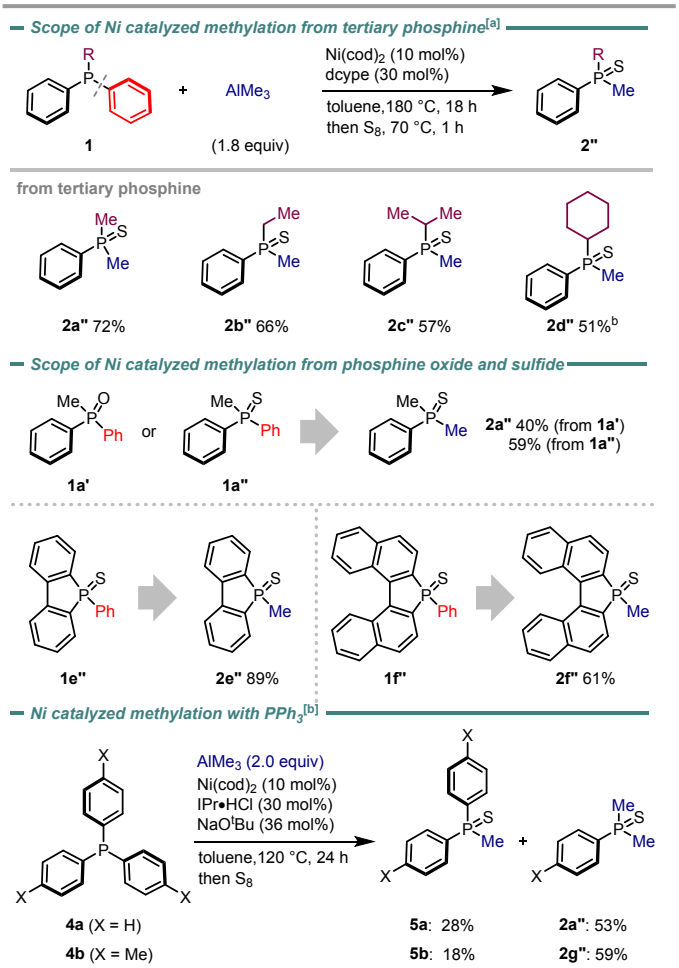


Figure 2 Scope of the nickel -catalyzed methylation of phosphine reagents

[a]Reaction conditions: phosphine **1** (0.15 mmol), $Ni(cod)_2$ (0.015 mmol), dcype (0.045 mmol) and $AlMe_3$ (0.30 mL) in toluene (0.3 mL) at 180 °C for 18 h. [b]Using 3.6 equiv of $AlMe_3$. [c]Reaction conditions: phosphine **4** (0.15 mmol), $Ni(cod)_2$ (0.015 mmol), IPr·HCl (0.045 mmol), NaO^tBu (0.054 mmol) and $AlMe_3$ (0.17 mL) in toluene (0.3 mL) at 180 °C for 18 h.

To gain insights into the nature of the interaction of the $AlMe_3$ reagent with the phosphine substrate, a mixture of **1a** and $AlMe_3$ (1.8 equiv) was monitored by ^{31}P NMR spectroscopy. This monitoring revealed that the chemical shift of **1a** shifted from ‑33.4 to ‑30.6 ppm upon the addition of $AlMe_3$ at ambient temperature, which is in agreement with the shift reported for the phosphine-aluminum adduct **1a-AlMe$_3$**[16] (Figure 3a). This result indicates that phosphine substrates immediately coordinate to $AlMe_3$ to form an adduct, which facilitates the activation of the C(aryl)–P bond. To examine the fate of the eliminated aryl fragment of the arylphosphine substrate, a substrate bearing a 4-biphenyl group (*i.e.*, **6**) was reacted under the Ni/IPr-catalyzed conditions and quenched with D_2O (Figure 3b). As a result, the mono-methylated (**7**) and di-methylated (**8**) phosphines were formed in 18% and 41% yield, respectively. In addition, 4-deuterated biphenyl **9** was produced in 70% yield (based on the converted biphenyl group), which was likely formed via the generation of the (4-biphenyl)Al species **D'**. We also monitored the crude reaction mixture by ^{31}P-NMR (Figure 3c). When the arylphosphine **1a** was used as a substrate, most of the methylated product **2a** was present as its aluminum adduct **2a-AlMe$_3$**. Interestingly, when the corresponding oxide **1a'** was used as the substrate, a mixture of **1a**/**2a**/**2a-AlMe$_3$** (1/0.7/4.1) was formed, and neither **1a'** nor **2a'** were observed. These results suggest that **1a'** is methylated

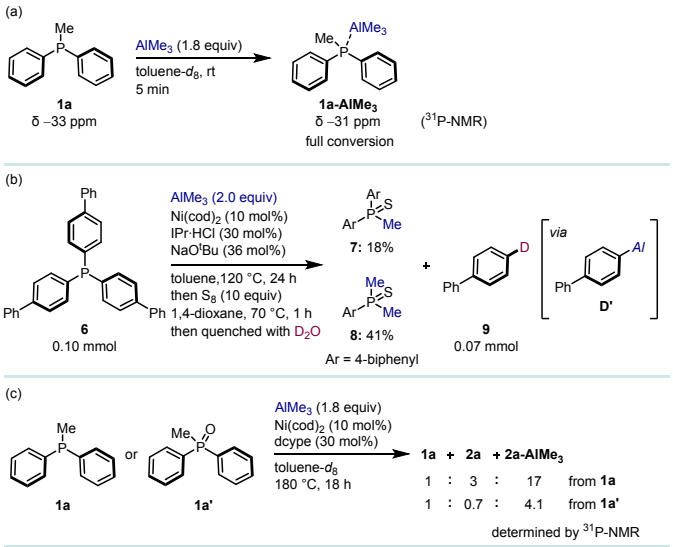


Figure 3 Mechanistic studies

after being reduced to trivalent phosphine **1a** under these catalytic conditions.

Based on the results shown in Figure 3, a possible mechanism is depicted in Figure 4. Initial formation of phosphine-aluminum adduct **1-AlMe$_3$** would reduce the electron density of the C(aryl)–P bond in **1**, thereby facilitating oxidative addition to a Ni(0) catalyst to form intermediate **A**.[17] A methyl group on the aluminum center in **A** is subsequently transferred to nickel via transmetallation to generate the Me–Ni–Ar intermediate **B** and aluminum phosphide **C**.[7] The formal nucleophilic attack by a phosphide fragment in **C** to the methyl group in **B** via a cyclic transition state **TS** results in the formation of methylated phosphine **2** and Ar–$AlMe_2$ **D** with the regeneration of Ni(0). The formation of **D** is supported by the detection of Ar–D upon quenching the reaction mixture with D_2O (Figure 2b). Intermediate **B** is supported by the observation of a trace amount of Me–Ar by GC-MS, which is likely formed by reductive elimination from **B**.[18] An alternative mechanism that involves a direct exchange between the aryl group on the nickel center and the methyl group on the aluminum center in **A** to generate Me–Ni–PMeAr and D cannot be excluded (see ESI for details).

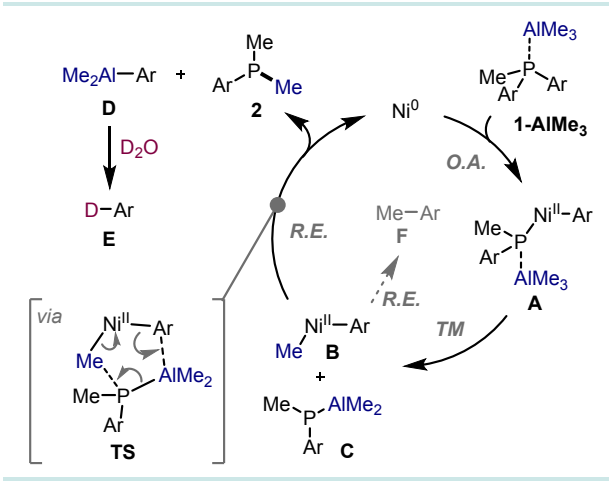


Figure 4 Proposed mechanism

In summary, we report on the direct, catalytic methylation of arylphosphine derivatives via the cleavage of a C(aryl)–P bond using $AlMe_3$. The use of $AlMe_3$ as a methylating reagent allows to avoid prior formation of a phosphonium salt. In addition to trivalent phosphines, phosphine oxides and sulfides can also be used directly in this nickel-catalyzed methylation reaction.

This work was supported by KAKENHI (JP21H04682 and JP17H06091) from MEXT, Japan. R.S. thanks JST SPRING (JPMJSP2138) for their support. We also thank the Instrumental Analysis Center, Faculty of Engineering, Osaka University, for assistance with HRMS.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 Selected reviews of phosphine organocatalysis: a) H. Guo, Y. C. Fan, Z. Sun, Y. Wu and O. Kwon, *Chem. Rev.*, 2018, **118**, 10049–10293; (b) H. Ni, W.-L. Chan and Y. Lu, *Chem. Rev.*, 2018, **118**, 9344–9411; (c) J. M. Lipshultz, G. Li and A. T. Radosevich, *J. Am. Chem. Soc.*, 2021, **143**, 1699–1721.; our works along this line: (d) H. Fujimoto, T. Kodama, M. Yamanaka and M. Tobisu, *J. Am. Chem. Soc.,* 2020, **142**, 17323–17328. (e) H. Fujimoto, M. Kusano, T. Kodama and M. Tobisu, *J. Am. Chem. Soc.*, 2021, **143**, 18394–18399. (f) H. Fujimoto, S. Yamamura, N. Takenaka and M. Tobisu, *Synthesis*, 2023, **55**, 899–906.

2 Selected reports of deoxygenation of carboxylic acids or nitro compounds with phosphine reagents: (a) E. E. Stache, A. B. Ertel, T. Rovis and A. G. Doyle, *ACS Catal.*, 2018, **8**, 11134–11139; (b) M. Zhang, J. Xie and C. Zhu, *Nat Commun*, 2018, **9**, 3517; (c) T. V. Nykaza, T. S. Harrison, A. Ghosh, R. A. Putnik and A. T. Radosevich, *J. Am. Chem. Soc.*, 2017, **139**, 6839–6842. (d) G. Li, T. V. Nykaza, J. C. Cooper, A. Ramirez, M. R. Luzung and A. T. Radosevich, *J. Am. Chem. Soc.*, 2020, **142**, 6786–6799. (e) G. Li, Z. Qin and A. T. Radosevich, *J. Am. Chem. Soc.*, 2020, **142**, 16205–16210. (f) G. Li, S. P. Miller and A. T. Radosevich, *J. Am. Chem. Soc.*, 2021, **143**, 14464–14469.

3 Selected reviews on phosphine ligands for transition metal complexes: a) R. Martin and S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1461–1473. (b) J.-H. Xie and Q.-L. Zhou, *Acc. Chem. Res.*, 2008, **41**, 581–593. (c) A. L. Clevenger, R. M. Stolley, J. Aderibigbe and J. Louie, *Chem. Rev.*, 2020, **120**, 6124–6196.

4 (a) I. Wauters, W. Debrouwer and C. V. Stevens, *Beilstein J. Org. Chem.*, 2014, **10**, 1064–1096. (b) L. Rout and T. Punniyamurthy, *Coord. Chem. Rev.*, 2021, **431**, 213675.

5 Selected works on aryl group exchange reactions of aryphosphines: (a) A. Nakamura and S. Otsuka, *Tetrahedron Lett.*, 1974, **15**, 463–466. (b) A. G. Abatjoglou and D. R. Bryant, *Organometallics*, 1984, **3**, 932–934. (c) M. Sakamoto, I. Shimizu, A. Yamamoto, *Chem. Lett.*, 1995, **24**, 1101-1102. (d) F. Y. Kwong and K. S. Chan, *Organometallics*, 2000, **19**, 2058–2060. (e) L. K. Hwang, Y. Na, J. Lee, Y. Do and S. Chang, *Angew. Chem. Int. Ed.*, 2005, **44**, 6166–6169. (f) Lian, B. N. Bhawal, P. Yu and B. Morandi, *Science*, 2017, **356**, 1059–1063. (g) X. Zhang and A. McNally, *Angew. Chem. Int. Ed.*, 2017, **56**, 9833–9836. (h) Y. H. Lee and B. Morandi, *Nature Chem*, 2018, **10**, 1016–1022. (i) Zhang and A. McNally, *ACS Catal.*, 2019, **9**, 4862–4866. (j) H. Wang, M. Yang, Y. Wang, X. Man, X. Lu, Z. Mou, Y. Luo and H. Liang, *Org. Lett.*, 2021, **23**, 8183–8188. Our previous works: (k) K. Baba, Y. Masuya, N. Chatani and M. Tobisu, *Chem. Lett.*, 2017, **46**, 1296–1299. (l) K. Baba, M. Tobisu and N. Chatani, *Org. Lett.*, 2015, **17**, 70–73. (m) K. Baba, M. Tobisu and N. Chatani, *Angew. Chem. Int. Ed.*, 2013, **52**, 11892–11895. (n) H. Fujimoto, M. Kusano, T. Kodama and M. Tobisu, *Org. Lett.*, 2019, **21**, 4177–4181. (*a*) R. Takise, R. Isshiki, K. Muto, K. Itami and J. Yamaguchi, *J. Am. Chem. Soc.*, 2017, **139**, 3340–3343. (*b*) Q. H. Luu and J. Li, *Chem. Sci.*, 2022, **13**, 1095–1100.

6 (a) A. M. Aguiar, J. Beisler and A. Mills, *J. Org. Chem.*, 1962, **27**, 1001–1005. (b) A. M. Aguiar, H. J. Greenberg and K. E. Rubenstein, *J. Org. Chem.*, 1963, **28**, 2091–2093. (c) J. Ye, J.-Q. Zhang, Y. Saga, S. Onozawa, S. Kobayashi, K. Sato, N. Fukaya and L.-B. Han, *Organometallics*, 2020, **39**, 2682–2694.

7 J. Tang, L. Ling, S. Yuan, M. Luo and X. Zeng, *Org. Lett.*, 2022, **24**, 1581–1586.

8 (a) M. Lei, X. Chen, Y. Wang, L. Zhang, H. Zhu and Z. Wang, *Org. Lett.*, 2022, **24**, 2868–2872. (b) S. Roediger, S. U. Leutenegger and B. Morandi, *Chem. Sci.*, 2022, **13**, 7914–7919.

9 (a) T. Morioka, A. Nishizawa, K. Nakamura, M. Tobisu and N. Chatani, *Chem. Lett.*, 2015, **44**, 1729–1731. (b) X. Liu, C. Hsiao, I. Kalvet, M. Leiendecker, L. Guo, F. Schoenebeck and M. Rueping, *Angew. Chem. Int. Ed.*, 2016, **55**, 6093–6098.

10 Y. Nakao, *Chem. Rev.*, 2021, **121**, 327–344.

11 See the SI for the details of optimization.

12 For detailed effect of the amount of $AlMe_3$ on the yield, see SI.

13 P. Finkbeiner, J. P. Hehn and C. Gnamm, *J. Med. Chem.*, 2020, **63**, 7081–7107.

14 M. Hayashi, *Chem. Lett.*, 2021, **50**, 1–6.

15 See the SI for the details of optimization.

16 R. Barron, *J. Chem. Soc., Dalton Trans.*, 1988, 3047.

17 Reviews on C–P bond activation by transition metal complexes: (a) M. Tobisu, T. Kodama and H. Fujimoto, in *Comprehensive Organometallic Chemistry IV*, eds. G. Parkin, K. Meyer and D. O'hare, Elsevier, Oxford, 2022, pp. 347-420. (b) H. Chen and Z. Duan, *Chem. Asian J.*, 2018, **13**, 2164–2173. (c) Garrou、P. E. *Chem. Rev.*, 1985, **85**, 171–185.

18 For instance, 4-methyl-1,1'-biphenyl was observed in the reaction using **6**. See SI for details.