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Phosphazene base *t*-Bu-P4-catalyzed methoxy–alkoxy exchange reaction on (hetero)arenes

Masanori Shigeno,*[a] Kazutoshi Hayashi,[a] Kanako Nozawa-Kumada,[a] and Yoshinori Kondo*[a]

Abstract: We herein describe that the organic superbase *t*-Bu-P4 catalyzes methoxy–alkoxy exchange reactions on (hetero)arenes with alcohols. The catalytic reaction proceeds efficiently with electron-deficient methoxy(hetero)arenes, as well as a variety of alcohols, including 3-amino-1-propanol, β-citronellol, menthol, and cholesterol. An intramolecular version of this reaction furnishes six- and seven-membered ring compounds.

Methoxyarenes are important structures in organic synthesis because of their widespread availability and application in various reactions including orthometallation[1] and electrophilic aromatic substitution.[2] Hence, development of the direct transformation of C(aryl)–OMe bonds is considered to be of great importance. However, because of the inertness of C(aryl)–OMe bonds, these reactions have limited scope as compared with those of C(aryl)–(pseudo)halogen bonds, such as transition-metal catalysis[3] and nucleophilic aromatic substitution (S_NAr).[4] For example, transition-metal complexes catalyze the transformation of the methoxy group on (hetero)arenes with carbon, hydride, amine, boron, and silane nucleophiles to form C–C,[5a-5d] C–H,[5e-5g] C–N,[5h] C–B,[5i] and C–Si bonds.[5j] As a result of the strict guidelines for trace amounts of transition metals in medicines and electronic functional materials, the development of a non-transition-metal system for methoxy-group conversion is imperative. Biswas and coworkers showed that TfOH catalyzes methoxy substitutions on electron-rich (hetero)arenes with nucleophiles by generating an electrophilic oxocarbenium intermediate from a methoxy(hetero)arene, which results in C–O, C–S, C–N, and C–C bond formations (Figure 1, a).[6] Nicewicz and coworkers demonstrated that acridinium photocatalysis promotes C–N bond forming reactions of methoxy(hetero)arenes with amines through a single-electron oxidation process (Figure 1, b).[7] As a complementary method, basic conditions with a stoichiometric amount of Brønsted base and pronucleophiles or pre-prepared anionic nucleophiles were found to be effective for methoxy substitution on arenes, forming C–C,[8] C–N,[9,10] and C–O bonds (Figure 1, c).[11] There is, however, essentially no report of Brønsted base-catalyzed methoxy substitutions with a wide substrate scope.[12]

We have previously reported that the organic superbase *t*-Bu-P4[13] can catalyze deprotonative transformations of heteroarenes, alcohols, and amines with electrophiles (carbonyls, heteroarene *N*-oxides, alkynes, epoxides, and fluoroarenes) through the effective activation of nucleophiles.[14-16] For example, *t*-Bu-P4 catalyzes the S_NAr reaction of fluoroarenes with alcohols in the presence of Et_3SiH.[14d] We herein wish to report that *t*-Bu-P4 allows a catalytic methoxy–alkoxy exchange reaction on (hetero)arenes in the presence of alcohols as nucleophiles (Figure 1, d). The obtained alkyl (hetero)aryl ether is a privileged motif in natural products, pharmaceutical compounds, and functional materials, and this has motivated organic chemists to develop the methodologies for its synthesis.[17,18] The present catalytic reaction is complementary to the well-studied methodologies using aryl (pseudo)halides as electrophiles, such as the Pd-catalyzed Buchwald/Hartwig[18c,19] and Cu-catalyzed Ullmann aryl ether formations[18h,19,20] or S_NAr reactions.[4,21] Our system is advantageous over the conventional reactions because it does not generate stoichiometric amounts of inorganic waste materials. The reaction proceeds efficiently in the case of methoxyarenes bearing electron-withdrawing cyano, keto, and aldehyde groups, as well as electron-deficient methoxyheteroarenes. The reaction allows the chemoselective introduction of a diverse array of alcohols bearing amine, ether, olefin, and sugar moieties.

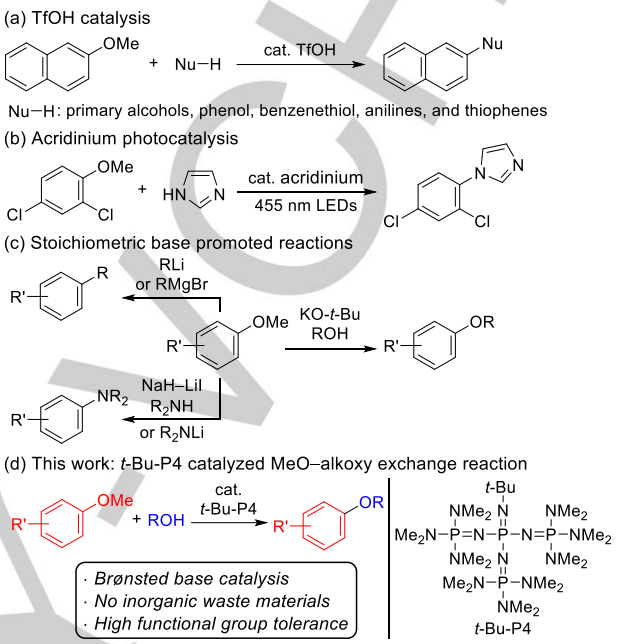

Figure 1. Transition-metal-free methoxy substitutions on arenes

Initially, the methoxy substitution reaction of 4-cyanoanisole (**1a**) with neopentyl alcohol (**2a**) was carried out in the presence of 20 mol % of *t*-Bu-P4 in THF (Table 1). The reaction of **1a** with 2 equivalents of **2a** at 90 ºC afforded the desired product **3aa** in 50% yield (entry 2). The reversibility of the reaction was confirmed by the treatment of **3aa** with 2 equivalents of MeOH under the

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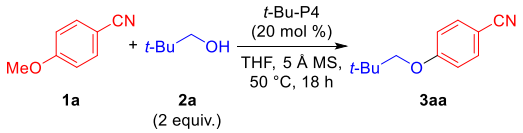
Table 1. Optimization of the reaction conditions[a]



Entry	Deviation from standard conditions	**3aa** (%)[b]
1	None	96
2	90 ºC, in the absence of 5Å MS	50
3	90 ºC, 4Å MS instead of 5Å MS	63
4	90 ºC	80
5	rt	(13)[c]
6	10 mol % of *t*-Bu-P4	52
7	6 h of reaction time	55
8	In the absence of *t*-Bu-P4	(0)[c]
9	1,4-dioxane as solvent	91
10	toluene as solvent	50

[a]Standard conditions: **1a** (0.20 mmol), **2a** (0.40 mmol), *t*-Bu-P4 (0.04 mmol), 5Å MS (70 mg), THF (0.7 mL), 50 ºC, 18 h. [b]Isolated yields. [c]The yields in parentheses were determined by ^{1}H-NMR spectroscopy with 1,1,2-trichloroethane as an internal standard.

same conditions to obtain **1a** (Scheme S1). The reaction of **1a** was then performed with molecular sieves in order to trap the generated MeOH and shift the equilibrium to the product side; this provided **3aa** in an increased yield of 80% with 5Å MS (entries 3 and 4). When the reaction temperature was lowered to 50 ºC, **3aa** was obtained in 96% yield (entries 1 and 5). Decreasing the catalytic amount of *t*-Bu-P4 to 10 mol % or shortening the reaction time to 6 h reduced the product yields (entries 6 and 7). In the absence of *t*-Bu-P4, **3aa** was not formed (entry 8). Use of 1,4-dioxane as a solvent also afforded **3aa** in a high yield of 91%, while that of toluene furnished a medium yield of 50% (entries 9 and 10). Other organic or inorganic Brønsted bases were ineffective for the reaction, thus confirming the critical role of *t*-Bu-P4 as the catalyst (Table S1). Deprotonation of alcohol by *t*-Bu-P4 generates an alkoxide and a large soft cation ([*t*-Bu-P4]$^+$H, ~500 Å^3); the naked alkoxide is extraordinarily reactive for the present reaction.[22]

With the optimized conditions in hand, we evaluated the scope of the methoxy(hetero)arenes that could be used in the reaction with **2a** (Figure 2). The reaction of 4-benzoylanisole (**1b**) proceeded to furnish **3ba** in 92% yield. Anisoles **1c** and **1d**, possessing formyl and pivaloyl groups, provided the corresponding products **3ca** and **3da** in 84% and 67% yields, respectively. Interestingly, 4-acetylanisole (**1e**) also provided the corresponding product in 56% yield, although it has an acidic C(sp^3)–H bond at the α-position of the carbonyl group.[23,24] The reaction of 4-nitroanisole (**1f**) proceeded at room temperature to give **3fa** in 74% yield. Halogen atoms (Cl and Br) were tolerated in the formation of **3ga** and **3ha**, respectively. The reaction of 2-cyanoanisole (**1i**) resulted into **3ia** in a low yield of 24%, whereas that of 3-cyanoanisole (**1j**) afforded a trace amount of product. In

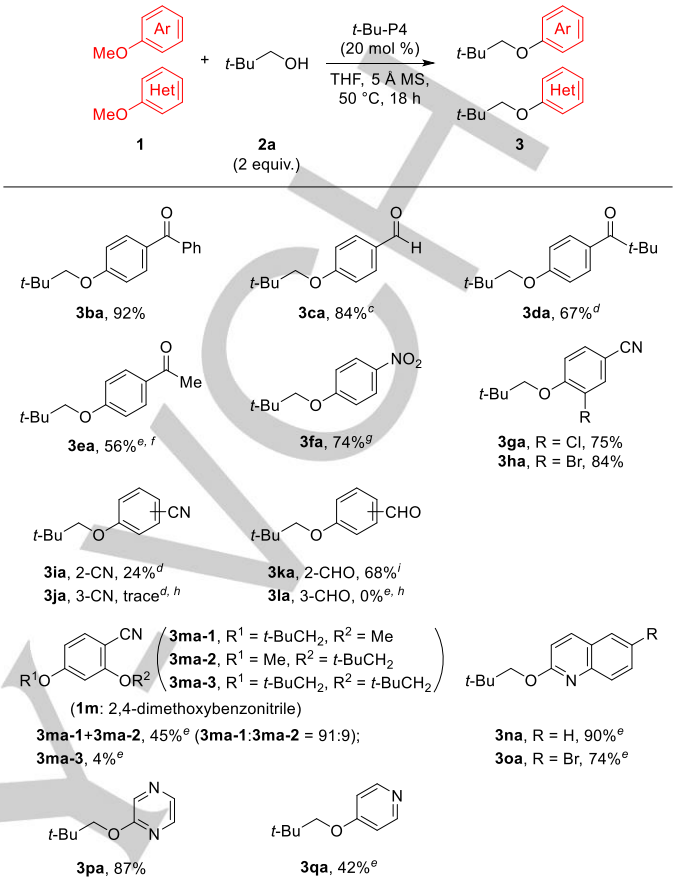


Figure 2. Scope of methoxy(hetero)arenes[a, b] [a]Reactions were conducted on a 0.2 mmol scale. [b]Isolated yields. [c]Reaction was conducted at 40 ºC. [d]Reaction was conducted in 1,4-dioxane at 120 ºC. [e]Reaction was conducted at 90 ºC. [f]Reaction was conducted for 12 h. [g]Reaction was conducted at room temperature. [h]Yield was determined by ^{1}H-NMR spectroscopic analysis. [i]Reaction was conducted at 80 ºC.

the cases of 2-formylanisole (**1k**) and 3-formylanisole (**1l**) as substrates, the former provided the product **3ka** in 68% yield; however, the latter did not form **3la**. In the reaction of 2,4-dimethoxybenzonitrile (**1m**), the methoxy substitution occurs mainly at the para-position of the cyano group to form a mixture of **3ma-1** and **3ma-2** in 45% yield (**3ma-1**:**3ma-2** = 91:9) along with the formation of **3ma-3** in 4% yield. Thus, the reactivity of the methoxyarenes is dependent on the position of an electron-withdrawing group and increases in the order of meta- < ortho- < para-position. This is probably because the stability of the cyclohexadienyl anion intermediate, formed by the nucleophilic attack of the alkoxide onto the methoxyarene, increases in that order.[4c,25]

Next, electron-deficient methoxyheteroarenes were employed in the reaction (Figure 2). 2-Methoxy-quinoline (**1n**) and 6-bromo-2-methoxy-quinoline (**1o**) afforded the corresponding products **3na** and **3oa** in 90% and 74% yields, respectively.[26] 2-Methoxypyrazine (**1p**) and 4-methoxypyridine (**1q**) provided the respective products in 87% and 42% yields.[27]

In the next phase of this study, the scope of the methoxy substitution was examined by using various alcohols (Figure 3).

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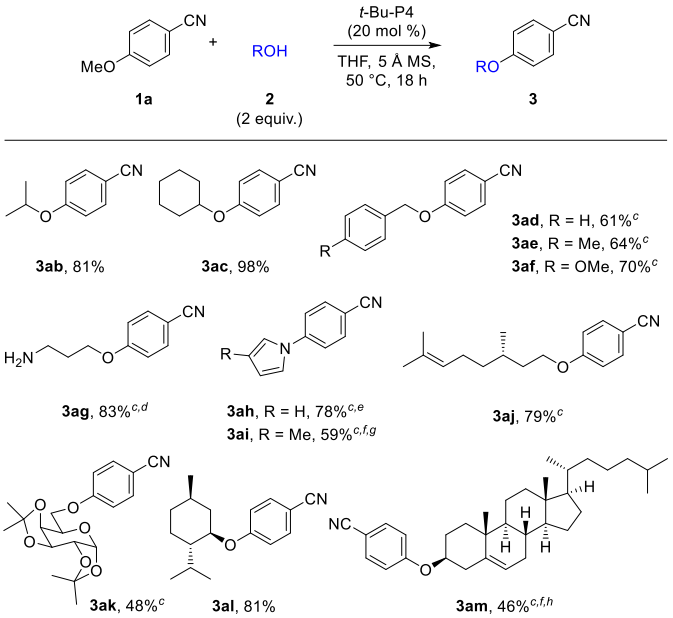
Figure 3. Scope of alcohols[a, b] [a]Reactions were conducted on a 0.2 mmol scale.



[b]Isolated yields. [c]Reaction was conducted at 90 ºC. [d]Product was isolated after acetylation of the amino group. [e]**2h** (3 equiv.) was used. [f]Reaction was conducted with *t*-Bu-P4 (30 mol %). [g]**2i** (3 equiv.) was used. [h]Reaction was conducted for 48 h.

The reactions with the secondary alcohols isopropyl alcohol (**2b**) and cyclohexanol (**2c**) proceeded to form **3ab** and **3ac** in high yields of 81% and 98%, respectively. Benzyl alcohols **2d**–**2f** underwent the methoxy substitution and afforded the corresponding products in 61%, 64%, and 70% yields, respectively.[28] In the case of 3-amino-1-propanol (**2g**), the reaction occurred chemoselectively at the hydroxy moiety to form ether **3ag**, which was isolated in 83% yield after acetylation of the amino group. In a related reaction, pyrrole (**2h**) and 3-methylpyrrole (**2i**) were employed as the nitrogen nucleophiles to provide **3ah** and **3ai** in 78% and 59% yields, respectively. (–)-β-Citronellol (**2j**), bearing an olefin moiety, also gave the corresponding product **3aj** in a good yield of 79%. Additionally, 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**2k**) and (–)-menthol (**2l**) could be used for the methoxy substitution in this protocol. Lastly, cholesterol (**2m**) was used for this reaction, affording the desired product **3am** in 46% yield.

An intramolecular variant of the present catalytic methoxy substitution was also demonstrated (Figure 4). The reactions of

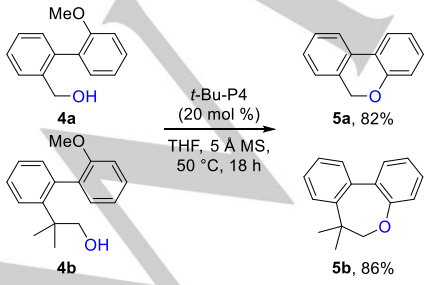


Figure 4. Intramolecular MeO–alkoxy exchange reaction[a, b] [a]Reactions were conducted on a 0.2 mmol scale. [b]Isolated yields.

4a and **4b** were carried out with 20 mol % of *t*-Bu-P4 to construct six- and seven-membered ring products in high yields of 82% and 86%, respectively.[29] In the catalytic intramolecular cyclization, electron-withdrawing groups were not required on the arenes.

A proposed mechanism for the *t*-Bu-P4-catalyzed methoxy–alkoxy exchange reaction is shown in Figure 5. Initially, *t*-Bu-P4 triggers the deprotonation of alcohol **2**. The high nucleophilicity of the generated alkoxide **A** facilitates methoxy–alkoxy exchange on (hetero)arenes **1** via an S_NAr process to form product **3**. Then, **B** reacts with **2** to regenerate **A**, with the concomitant formation of MeOH.

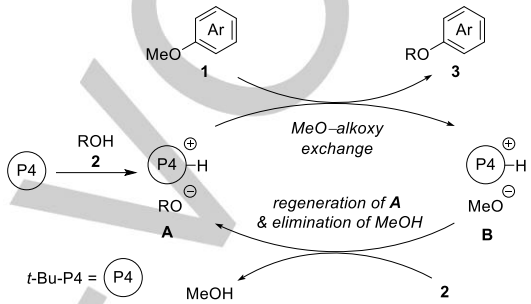


Figure 5. Proposed mechanism

In summary, we have developed a *t*-Bu-P4-catalyzed methoxy–alkoxy exchange reaction on (hetero)arenes with cyano, formyl, (non)enolizable ketonic carbonyl, and halo groups to form alkoxy (hetero)arenes. Various alcohols bearing amine, ether, olefin, and sugar moieties participated in the reaction to furnish the desired products. The application of this protocol to an intramolecular reaction was also demonstrated by using non-activated substrates without an electron-withdrawing group to form six- and seven-membered ring skeletons.

Acknowledgements

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Keywords: Phosphazenes • Methoxyarenes • Aromatic substitution • Alcohols • Organocatalysis

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[21] Williamson reaction, using alkyl (pseudo)halides and phenols, is a common approach for the synthesis of alkyl aryl ethers. Developments of the methodologies using alcohols as nucleophiles are, however, also important from the following viewpoints: alcohols are usually readily available compared with the corresponding alkyl (pseudo)halides; in the Williamson reaction E2 elimination often occurs, particularly for sterically hindered secondary alkyl (pseudo)halides, as a side reaction.

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[23] pKa value for the $C(cp^3)$–H bond at the α-position of carbonyl of **1e** is 25.6 (a) F. G. Bordwell, F. J. Cornforth, *J. Org. Chem.* **1978**, *43*, 1763. For comparison, pKa value for the O–H bond of EtOH is 29.8. (b) W. N. Olmstead, Z. Margolin, F. G. Bordwell, *J. Org. Chem.* **1980**, *45*, 3295.

[24] In the recent report of methoxy–alkoxy exchange reaction on methoxyarenes using a stoichiometric amount of KO-*t*-Bu,[11a] carbonyl groups (formyl, benzoyl, and acetyl) could not be used instead of a cyano group as an activating group on methoxy arenes.

[25] For the related discussion, see: A. J. Birch, A. L. Hinde, L. Radom, *J. Am. Chem. Soc.* **1980**, *102*, 6430.

[26] It was previously reported that several methoxy heteroarenes such as benzothiazole-,[26a, 26b] quinazoline-,[26b] cinnoline-,[26b] and phthalazine-derivatives,[26b] reacted with alcohols by using stoichiometric amounts of NaOH, KOH, or Na-alkoxides, which was, however, inapplicable to the reaction of quinoline-derivative.[26b] (a) H. H. Fox, M. T. Bogert, *J. Am. Chem. Soc.* **1941**, *63*, 2996. (b) K. Adachi, *Yakugaku Zasshi* **1955**, *75*, 1426.

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[27] In the reaction of an electron-deficient heteroarene of **1p** with **2a**, organic Brønsted bases of proton sponge (1,8-bis-(dimethylamino)naphthalene), DBU (1,8-diazabicyclo[5.4.0]-7-undecene), TBD (1,5,7-triazabicyclo-[4.4.0]dec-5-ene), and *t*-Bu-P2 (1-(*tert*-butylimino)-1,1,3,3,3-pentakis(dimethylamino)-1λ5, 3λ5-diphosphazene) were employed as a catalyst instead of *t*-Bu-P4, however, no desired product **3pa** was obtained (results not shown).

[28] In the reactions affording **3ad**, **3ae**, and **3af**, dibenzyl ether, bis(*p*-methylbenzyl) ether, and bis(*p*-methoxylbenzyl) ether were also formed in the NMR yields of 2%, 5%, and 3%, respectively.

[29] It was previously reported that a stoichiometric amount of Bønsted bases promotes intramolecular methoxy-alkoxy exchange reactions to form five- and six-membered ring products, see: (a) N. Ogawa, Y. Yamaoka, K. Yamada, K. Takasu, *Org. Lett.*, **2017**, 19, 3327. (b) L. Zhi, J. D. Ringgenberg, J. P. Edwards, C. M. Tegley, S. J. West, B. Pio, M. Motamedi, T. K. Jones, K. B. Marschke, D. E. Mais, W. T. Schrader, *Bio. Med. Chem. Lett.*, **2003**, *13*, 2075.

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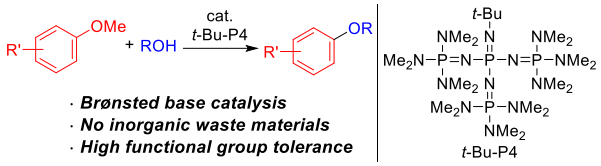

Masanori Shigeno, Kazutoshi Hayashi, Kanako Nozawa-Kumada, and Yoshinori Kondo**

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Phosphazene base *t*-Bu-P4-catalyzed methoxy–alkoxy exchange reaction on (hetero)arenes

The organic superbase *t*-Bu-P4 catalyzes methoxy–alkoxy exchange reactions on (hetero)arenes with alcohols. The catalytic reaction proceeds efficiently with electron-deficient methoxy(hetero)arenes, as well as a variety of alcohols, including 3-amino-1-propanol, β-citronellol, menthol, and cholesterol. An intramolecular version of this reaction furnishes six- and seven-membered ring compounds.