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Notes

Oxovanadium(V)-Induced Oxidative Ligand Coupling of Aryltrimethylzincates Prepared from Bromoarenes and Dilithium Tetramethylzincate

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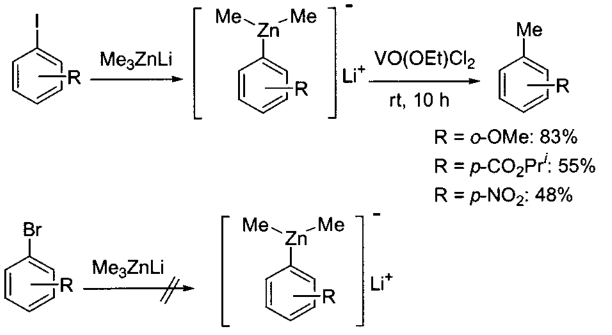
Oxidative transformation of main-group organometallics has been expected to develop the selective carbon−carbon bond forming reaction between two ligands on their metals.[1,2] We have already reported that the selective ligand coupling of organoaluminums, organoborons, organozincs, and/or their ate complexes is induced by oxovanadium(V) compounds as oxidants.[3] Although aryl−aryl homocoupling compounds are occasionally formed as byproducts in these coupling reactions, depending on the reaction conditions, use of iodine−zinc exchange[4] of iodoarenes with Me_3ZnLi suppresses such an aryl−aryl coupling of aryldimethylzincates,[3c] to give methylarenes[5] chemoselectively (Scheme 1). However, the coupling reaction is only applied to iodoarene, because the similar halogen−zinc exchange reaction with Me_3ZnLi does not proceed with bromoarenes. Recently, Uchiyama et al. demonstrated that dilithium tetramethylzincate, Me_4ZnLi_2, is effective for the chemoselective bromine−zinc exchange of *p*-substituted bromoarenes.[6] These results prompted us to investigate the oxovanadium(V)-induced coupling reaction of the organozincates, prepared from various bromoarenes and Me_4ZnLi_2.

Scheme 1



R = *o*-OMe: 83%
R = *p*-CO$_2$Pr^i: 55%
R = *p*-NO$_2$: 48%

Scheme 2

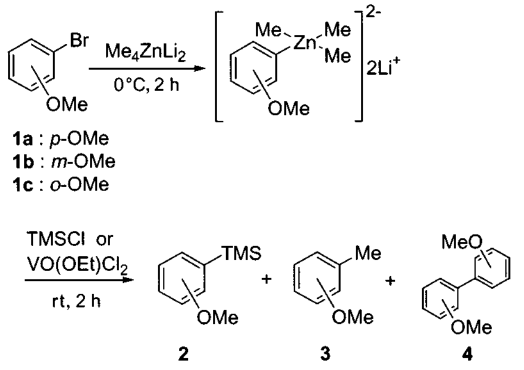


Table 1. Reactivities of 1 in Scheme 2

			yield (%)[b]		
entry	**1**	additive[a]	**2**	**3**	**4**
1	**1a**	TMSCl	98	−	−
2[c]	**1b**	TMSCl	−	−	−
3	**1c**	TMSCl	52	39	−
4	**1a**	$VO(OEt)Cl_2$	−	34	45
5	**1c**	$VO(OEt)Cl_2$	−	86	−

[a] TMSCl (10.0 equiv); $VO(OEt)Cl_2$ (3.0 equiv). [b] ^{1}H NMR yield. [c] **1b** was recovered quantitatively.

The reactivities of Me_4ZnLi_2 toward *o*-, *m*-, and *p*-bromoanisoles were first examined by quenching with chlorotrimethylsilane (Scheme 2). As shown in Table 1, the bromine−zinc exchange reaction of *p*-bromoanisole (**1a**) with Me_4ZnLi_2 proceeded smoothly in THF at 0 °C for 2 h to yield *p*-trimethylsilylanisole quantitatively (entry 1).[6] On the other hand, the reaction of *m*-bromoanisole (**1b**) led to the recovery of the starting mate-

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(1) For cupper(I)-induced oxidative coupling reactions of organoborons and organozincs, see: (a) Yamamoto, Y.; Yatagai, H.; Maruyama, K.; Sonoda, A.; Murahashi, S. *J. Am. Chem. Soc.* **1977**, *99*, 5652. (b) Iyoda, M.; Kabir, S. M. H.; Vorasingha, A.; Kuwatani, Y.; Yoshida, M. *Tetrahedron Lett.* **1998**, *39*, 5393.

(2) Oxidative tranformation of d^0 organometallics was also reported, see: (a) Jordan, R. F.; LaPointe, R. E.; Bajgure, C. S.; Echols, S. F.; Willet, R. *J. Am. Chem. Soc.* **1987**, *109*, 4111. (b) Borkowsky, S. L.; Baenziger, N. C.; Jordan, R. F. *Organometallics* **1993**, *12*, 486. (c) Burk, M. J.; Tumas, W.; Ward, M. D.; Wheeler, D. R. *J. Am. Chem. Soc.* **1990**, *112*, 6133. (d) Sato, M.; Mogi, E.; Kumakura, S. *Organometallics* **1995**, *14*, 3157. (e) Hayashi, Y.; Osawa, M.; Wakatsuki, Y. *J. Organomet. Chem.* **1997**, *542*, 241.

(3) (a) Ishikawa, T.; Ogawa, A.; Hirao, T. *J. Am. Chem. Soc.* **1998**, *120*, 5124. (b) Ishikawa, T.; Nonaka, S.; Ogawa, A.; Hirao, T. *J. Chem. Soc., Chem. Commun.* **1998**, 1209. (c) Hirao, T.; Takada, T.; Ogawa, A. *J. Org. Chem.* **2000**, *65*, 1511. Oxidative tranformation of organozirconiums as d^0 organometallics was also reported, see: (d) Ishikawa, T.; Ogawa, A.; Hirao, T. *J. Organomet. Chem.* **1999**, *575*, 76.

(4) Kondo, Y.; Takazawa, N.; Yamazaki, C.; Sakamoto, T. *J. Org. Chem.* **1994**, *59*, 4717.

(5) Other methylation method of haloarene was reported. For some examples for transition metal catalyzed cross-coupling of organometallics, see: (a) Hossain, M. K.; Takagi, K. *Chem Lett.* **1999**, 1241. (b) Blum, J.; Gelman, D.; Baidossi, W.; Shakh, E.; Rosenfeld, A.; Aizenshtat, Z.; Wassermann, B. C.; Frick, M.; Heymer, B.; Schutte, S.; Wernik, S.; Schumann, H. *J. Org. Chem.* **1997**, *62*, 8681. (c) Kondo, Y.; Matsudaira, T.; Sato, J.; Murata, N.; Sakamoto, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 736. (d) Kauffmann, T.; Nienaber, H. *Synthesis* **1995**, 207. (e) Vedejs, E.; Haight, A. R.; Moss, W. O. *J. Am. Chem. Soc.* **1992**, *114*, 6556. For some examples for methylation of aryllithium with methylhalide, see: (f) Ebdrup, S. *Synthesis* **1998**, 1107. (g) Ebert, G. W.; Pfenning, D. R. *Tetrahedron Lett.* **1993**, *34*, 2279. (h) Suchan, S. D.; Donovan, T. A., Jr. *Tetrahedron Lett.* **1990**, *31*, 4129. (i) Morrell, D. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1975**, *97*, 7262.

(6) (a) Uchiyama, M.; Kameda, M.; Mishima, O.; Yokoyama, N.; Koike, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 4934. (b) Uchiyama, M.; Koike, M.; Kameda, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1996**, *118*, 8733.

10.1021/jo000976u CCC: $20.00

Scheme 3

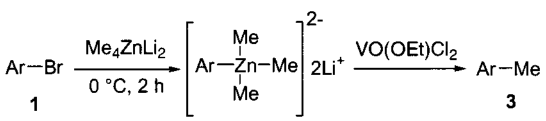
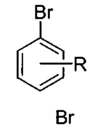
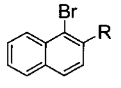
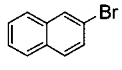
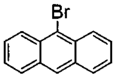


Table 2. Oxovanadium(V)-Induced Methylation of Aryltrimethylzincates

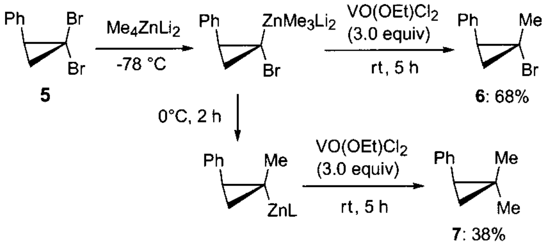
entry	1		R	time[a] (h)	isolated yield (%) of 3
1		**1c**	*o*-OMe	5	**3c** 82
2		**1d**	*o*-Ph	15	**3d** 99
3		**1e**	*o*-SMe	5	**3e** 97
4		**1f**	*o*-CN	15	**3f** 51
5		**1g**	*o,p*-OMe	5	**3g** 78
6		**1h**	*o*-OMe	5	**3h** 98
7		**1i**	H	5	**3i** 81
8		**1j**		5	**3j** 74
9		**1k**		5	**3k** 86

[a] $VO(OEt)Cl_2$ (3.0 equiv) was used. Reaction time for the oxidation with $VO(OEt)Cl_2$ at room temperature.

rial, indicating that the exchange reaction did not occur under the conditions employed here (entry 2). As for *o*-bromoanisole (**1c**), formal nucleophilic substitution was observed to give *o*-methoxytoluene in 39% yield, together with *o*-trimethylsilylanisole in 52% yield (entry 3).[7] Next, $VO(OEt)Cl_2$ was employed to oxidize the thus-obtained aryltrimethylzincates under the conditions mentioned above. Starting from **1a**, both methylarene and biaryl were produced in 34% and 45% yields, respectively (entry 4), whereas the expected methylarene was exclusively obtained in 86% yield in the case of **1c** (entry 5). Although the mechanism is not clear, the reaction is presumed to proceed by a process of either one-electron oxidation between the organozincate complex and oxovanadium(V) compound or transmetalation, as already proposed in the coupling reaction of triorganozincates.[3c,9]

Some representative results of the oxidative coupling reaction using the zincates derived from various bromoarenes and Me_4ZnLi_2 are shown in Scheme 3 and Table 2. *ortho*-Substituted bromoarenes having methoxy, phenyl, methylthio, or cyano groups underwent the methylation via the zincates to give the desired products in good yields (entries 1−4).[9] The zincates prepared from bromonaphthalene and bromoanthracene derivatives were also oxidized to the corresponding methylated arenes (entries 6−9). Thus, the coupling between sp^2-carbon (aryl group) and sp^3-carbon (methyl group) on aryltrimethylzincates is achieved chemoselectively.

Scheme 4



This oxidative coupling can be applied to the methylation reaction of 2-phenyl-1,1-dibromocyclopropane (**5**).[10] A bromine−zinc exchange reaction occurred at the position *cis* to the phenyl group selectively by treatment with Me_4ZnLi_2 at −78 °C. The oxidation of the thus-obtained zincate with $VO(OEt)Cl_2$ led to the stereoselective formation of (*E*)-1-bromo-1-methyl-2-phenylcyclopropane (**6**) in 68% yield. On the other hand, when the reaction mixture was warmed to 0 °C before treatment with $VO(OEt)Cl_2$, dimethylation took place to give the dimethylcyclopropane **7** (Scheme 4).

As described above, a combination of Me_4ZnLi_2 and $VO(OEt)Cl_2$ provides a new synthetic method for the methylation of bromoarene, which is less reactive than iodobenzene, and a first ligand coupling is also achieved between two sp^3-carbons, cyclopropyl and methyl groups of the methylcyclopropylzincate prepared from *gem*-dibromocyclopropane derivative.

Experimental Section

General Methods. All reagents are of commercial quality. All solvents were freshly distilled under argon over an appropriate drying agent before use. All procedures were carried out under argon. The bromonaphthalene **1h**[11] and dichloroethoxy oxovanadium(V)[3c,12] were prepared according to the literature procedures. Me_4ZnLi_2 was prepared as follows:[6] MeLi (1.02 M ether solution, 2.0 mL, 2.0 mmol) was added to a solution of $ZnCl_2$ (68 mg, 0.50 mmol) in THF (1 mL) under argon atmosphere at 0 °C, and the mixture was stirred for 30 min at 0 °C.

Representative Procedure for Oxidative Coupling Reaction of Aryltrimethylzincate (Table 2). To a stirred solution of the aryl bromide **1c** (94 mg, 0.50 mmol) in THF (1.0 mL) at room temperature was added Me_4ZnLi_2 (0.75 mmol) to generate the corresponding arylzincate. After stirring for 2 h at 0 °C, $VO(OEt)Cl_2$ (274 mg, 1.5 mmol) was added to a solution of the resulting zincate at 0 °C. The mixture was stirred for 5 h at room temperature, and then ether and 1.5 M aqueous HCl were added to the reaction mixture. After extraction with ether, the combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with hexane−ether (4:1) to give **3c** (50 mg, 82%, $R_f = 0.6$). The products were identified by comparison of ^1H NMR spectral data with those of the authentic samples.

2-Methylanisole (3c) [578-58-5]; **2-phenyltoluene (3d)** [643-58-3]; **1-methyl-2-(methylthio)benzene (3e)** [14092-00-3]; ***o*-tolunitrile (3f)** [529-19-1]; **2,4-dimethoxyltoluene (3g)** [38064-90-3]; **2-methoxy-1-methylnaphthalene (3h)** [1130-80-9]; **1-methylnaphthalene (3i)** [90-12-0]; **2-methylnaphthalene (3j)** [91-57-6]; **9-methylanthracene (3k)** [779-62-2].

Procedures for Oxidative Coupling to (*E*)-1-Bromo-1-methyl-2-phenylcyclopropane (6) or 1,1-Dimethyl-2-

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[7] Methylation of **1c** in the absense of $VO(OEt)Cl_2$ might proceed by the reaction of the bromoarene and MeLi, which is generated from Me_4ZnLi_2 in equilibration.[8] For methylation of *o*-substituted bromoarenes with MeLi or Me_2CuLi, see: (a) Patterson, J. W. *J. Org. Chem.* **1995**, *60*, 4542. (b) Ashby, E. C.; Lin, J. J. *J. Org. Chem.* **1977**, *42*, 2805.

[8] Mobley, T. A.; Berger, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3070.

[9] The only information about the reaction mechanism is that oxovanadium(V) compound is finally converted to oxovanadium(IV) species detected by ESR measurement. However, the experimental results cannot differentiate the two possible mechanisms, transmetalation of zincate with oxovanadium(V) compound or one-electron oxidation between arylzincate and oxovanadium(V). The ortho effect in Table 2 also remains unclarified from these reasons, although electric or steric interaction might be operating.

[10] For stereoselective alkylations of *gem*-dibromocyclopropanes with organozincates, see: Harada, T.; Katsuhira, T.; Hattori, K.; Oku, A. *J. Org. Chem.* **1993**, *58*, 2958 and references therein.

[11] Onoda, M.; Kawai, M.; Izumi, Y. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1761.

[12] (a) Funk, H.; Weiss, W.; Zeising, M. *Z. Anorg. Allg. Chem.* **1958**, *36*, 296. (b) Hirao, T.; Mori, M.; Ohshiro, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2399.

phenylcyclopropane (7). To a stirred solution of the dibromocyclopropane **5** (275 mg, 1.0 mmol) in THF (2.0 mL) at −78 °C was added Me_4ZnLi_2 (1.2 mmol). After 3 h of stirring at −78 °C, $VO(OEt)Cl_2$ (549 mg, 3.0 mmol) was added to a solution of the resulting zincate at 0 °C. The mixture was stirred for 10 h at room temperature, and then ether and 1.5 M aqueous HCl were added to the reaction mixture. After extraction with ether, the combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with hexane to give **6** (144 mg, 68%, $R_f = 0.4$). In the case of **7**, stirring was continued for 1 h at −78 °C and 2 h at 0 °C after Me_4ZnLi_2 was added, and then the following procedure was carried out as mentioned above, giving **7** (56 mg, 38%, $R_f = 0.5$). The products were identified by ^1H and ^{13}C NMR spectral data, and the relative configuration was determined by a NOESY experiment of **6**; **6** [55027-61-7]; **7** [7653-94-3].

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